AR201-14045B

**PHYSICAL/CHEMICAL ELEMENTS**
**1. MELTING POINT**

## TEST SUBSTANCE

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** No information on source/purity of test material

## METHOD

- **Method/guideline:** Japanese MITI test
- **GLP:** No data, but likely to be GLP
- **Year:** 1992

**Remarks:**

## RESULTS

- **Melting point value in °C:** 111-113
- **Decomposition:** No data
- **Sublimation:** No data

**Remarks:**

## CONCLUSIONS

**Remarks:**

## DATA QUALITY

- **Reliabilities:** 2, Valid with restrictions

**Remarks:** Peer reviewed study, limited information available

## REFERENCES (Free Text)

Chemicals and Testing Institute, Biodegradation and Bioaccumulation Data of existing Chemicals, Based on the CSCL Japan, Japan Chemical Industry Ecology-Toxicology and Information Center, ISBN 4-89074-101-1 (1992)

## OTHER

- **Last Changed:** October 3 2002
- **Order number for sorting:** 1

**Remarks:**
-

**PHYSICAL/CHEMICAL ELEMENTS**
**3. VAPOUR PRESSURE**

## TEST SUBSTANCE

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:**

## METHOD

- Method/guideline: Calculated
- GLP: No
- Year: 2002

**Remarks:** Calculated using MPBPWIN v1.31

## RESULTS

- **Vapour pressure value:** 1.3 x $10^{-5}$ mm Hg (1.7 x $10^{-3}$ Pa)
- **Temperature °C:** 25
- **Decomposition:** No applicable

**Remarks:**

## CONCLUSIONS

**Remarks:**

## DATA QUALITY

- 4, Not Assignable

**Remarks:** Estimation using MPBPWIN

## REFERENCES (Free Text)

MPBPWIN v1.31. EPIWIN modelling program. Meylan, W. & Howard, P. (1999), Syracuse Research Corporation, Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510

## OTHER

- **Last Changed:** October 3 2002
- **Order number for sorting:** 1

**Remarks:**

**PHYSICAL/CHEMICAL ELEMENTS**
**4. PARTITION COEFFICIENT**

## TEST SUBSTANCE

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** No information on source/purity of test material

## METHOD

- **Method/guideline:** Japanese MITI test
- **GLP:** No data, but likely to be GLP
- **Year:** 1992

**Remarks:**

## RESULTS

- **Log Pow:** 2.29
- **Temperature °C:** Not stated

**Remarks:**

## CONCLUSIONS

**Remarks:**

## DATA QUALITY

- **Reliabilities:** 2, Valid with restrictions

**Remarks:** Peer reviewed study, limited information available

## REFERENCES (Free Text)

Chemicals and Testing Institute, Biodegradation a nd Bioaccumulation Data of existing Chemicals, Based on the CSCL Japan, Japan Chemical Industry Ecology-Toxicology and Information Center, ISBN 4-89074-101-1 (1992)

## OTHER

- **Last Changed:** October 3 2002
- **Order number for sorting:** 1

**Remarks:**

## ENVIRONMENTAL FATE ELEMENTS AND PATHWAYS
## 9. BIODEGRADATION

### TEST SUBSTANCE

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** No information on source/purity of test material

### METHOD

- **Method/guideline:** Japanese MITI test
- **Test Type:** Aerobic
- **GLP:** No data, but likely to be GLP
- **Year:** 1992
- **Contact time (units):** 28 days
- **Innoculum:** Activated sewage sludge

**Remarks:**

- **Innoculum (concentration and source)**
  - **Fresh activated sludge:** 30 mg/l

- **Concentration of test chemical:** 100 mg/l
- **Temperature of incubation °C:** No data
- **Dosing procedure:** No data
- **Sampling frequency:** No data
- **Appropriate controls and blank system used?:** No data
- **Analytical method used to measure biodegradation:** No data
- **Method of calculating measured concentrations:** No data

### RESULTS

- **Degradation % after time:** 3 – 33% by BOD after 28 days
- **Results:** Not readily biodegradable
- **Kinetic:** No data

**Breakdown products (yes/no):** No data

**Remarks:**

### CONCLUSIONS

**Remarks:** Based on this test, the substance is not readily biodegradable

### DATA QUALITY

- **Reliabilities:** 2, Valid with restrictions

**Remarks:** Peer reviewed study, limited information available

**REFERENCES (Free Text)**

Chemicals and Testing Institute, Biodegradation and Bioaccumulation Data of existing Chemicals, Based on the CSCL Japan, Japan Chemical Industry Ecology-Toxicology and Information Center, ISBN 4-89074-101-1 (1992)

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 1

**Remarks:**

## HUMAN HEALTH ENDPOINTS
## 13.1 ACUTE TOXICITY

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Bromine Compounds Ltd.
Lot No.: 3456, Purity: 98.96%

**METHOD**

- **Method:** OECD 401
- **Test Type:** OECD single dose oral toxicity (limit) test
- **GLP:** Yes
- **Year:** 1992
- **Species/strain:** Rat, Sprague-Dawley
- **Sex:** Male/female
- **No. of animals/sex/dose:** Range finding study: 1 male, 1 female
  Main study: 5 males, 5 females
- **Vehicle:** Arachis oil
- **Route of administration:** Oral (single dose gavage)

**Remarks:**

- **Age:** 5 – 8 weeks old (bodyweight 136 – 153g males, 136 – 146g females)
- **Doses:** 2000 mg/kg
- **Volume administered:** 10 ml/kg
- **Post dose observation period:** Range finding study: 5 days
  Main study: 14 days

**RESULTS**

- **LD50:** > 2000 mg/kg bodyweight
- **Number of deaths at each dose level:**
  Range finding study: No deaths
  Main study: See Table 1. Three animals (one male and two females) were found dead after dosing at 2000 mg/kg.

**Remarks:**

- **Time of death:** Main study: Two females died 30 minutes after dosing. One male died one hour after dosing.
- **Clinical signs at each dose level:**
  Range finding study: Common signs of systemic toxicity noted were hunched posture, lethargy, ataxia, laboured respiration, decreased respiratory rate and ptosis with additional signs of pilo-erection, loss of righting reflex, red/brown staining around the eyes, vocalisation and increased lachrymation.

  Main study: See Table 1. Common signs of systemic toxicity noted were coma, laboured respiration, hunched posture and lethargy with additional signs of ataxia, ptosis and decreased respiratory rate.

Isolated incidents of loss of righting reflex were noted in two animals. Surviving animals appeared normal one or two days after dosing.

Table 1: Individual clinical observations and mortality data

| Dose Level mg/kg | Animal number & sex | Effect noted after dosing (hours) | | | | Effects noted after dosing (days) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 1/2 | 1 | 2 | 4 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| 2000 | 3-0 male | Co,Rl | X | | | | | | | | | | | | | | | | |
| | 3-1 male | H,L,A,Rl | H,L,A,Rl | H,L,A.Rl | H,L | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3-2 male | Co,Rl | Co,Pt Rl,Rd | Rr,Rl,Rd | H,L | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3-3 male | H,L,A,Rl | H,L,A Rl,Pt | H,L,A Rl,Pt | H,L | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 3-4 male | Co,Rl | Co,Rl,Rd | Co,Rl,Rd | Co,Pt Rd,Pt | H,L | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 4-0 female | X | | | | | | | | | | | | | | | | | |
| | 4-1 female | Co,Rl | Co,Rl,Rd | Co,Rl Rd,Pt | Co,Pt Rd,Rl | H,L | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 4-2 female | H,L,A | H,L,A,Rl | H,L,A,Rl | H,L,A | L | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 4-3 female | Rr,L,Rl | Rr,Rl,Rd | H,L,A,Rl | H,L,Rl,A | L | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 4-4 female | X | | | | | | | | | | | | | | | | | |

A – ataxia, Co – coma, H – hunched posture, L – lethargy, Pt – ptosis, Rd – decreased respiratory rate, Rl – laboured respiration, Rr – loss of righting reflex, 0 – no signs of systemic toxicity, X – animal dead

- **Necropsy findings:** See Table 2. Abnormalities noted at necropsy of animals that died during the study were dark liver, dark kidneys and slight haemorrhage of the gastric mucosa. No abnormalities were noted at necropsy of animals that were killed at the end of the study.

Table 2: Individual necropsy findings

| Dose Level mg/kg | Animal Number & Sex | Time of Death | Macroscopic Observations |
|---|---|---|---|
| 2000 | 3-0 male | Found dead day 0 | Liver: dark<br>Kidneys: dark<br>Gastric mucosa: slight haemorrhage |
| | 3-1 male | Killed day 14 | No abnormalities detected |
| | 3-2 male | Killed day 14 | No abnormalities detected |
| | 3-3 male | Killed day 14 | No abnormalities detected |
| | 3-4 male | Killed day 14 | No abnormalities detected |
| | 4-0 female | Found dead day 0 | Liver: dark<br>Kidneys: dark<br>Gastric mucosa: slight haemorrhage |
| | 4-1 female | Killed day 14 | No abnormalities detected |
| | 4-2 female | Killed day 14 | No abnormalities detected |
| | 4-3 female | Killed day 14 | No abnormalities detected |
| | 4-4 female | Found dead day 0 | Liver: dark<br>Kidneys: dark |

**CONCLUSIONS**

**Remarks:**

**DATA QUALITY**

- **Reliabilities:** 1, Reliable without restriction

**Remarks:** Study conducted under GLP to OECD test guideline by SafePharm Laboratories Ltd.

**REFERENCES (Free Text)**

SafePharm Laboratories Ltd., DBNPG (Dibromoneopentyl glycol): Acute oral toxicity (Limit test) in the rat, Report No. 466/3, June 1992

**OTHER**

- **Last Changed:** October 3, 2002
- **Order number for sorting:** 1

**Remarks:**

## HUMAN HEALTH ENDPOINTS
## 13.2 ACUTE TOXICITY

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dead Sea Bromine Company Ltd

**METHOD**

- **Method/guideline followed:** Similar to OECD 401
- **Type:** Oral gavage $LD_{50}$ study in rat
- **GLP:** No, but appears to be conducted to GLP principles
- **Year:** 1979
- **Species/strain:** Rat, CD strain
- **Sex:** Male/female
- **No of animals/sex/dose:** 5 male, 5 female per dose group
- **Vehicle:** Distilled water
- **Route of administration:** Oral (single dose gavage)

**Remarks:**

- **Age:** Approximately 35 days old (bodyweight 111 – 144g males, 106 – 129g females)
- **Doses:** 1247, 1484, 1765, 2101, 2500 mg/kg
- **Volume administered or concentration:** 20 ml/kg
- **Post dose observation period:** 14 days

**RESULTS**

- **LD50:** 1880 mg/kg, 95% confidence limits 1691 – 2120 mg/kg
- **Number of deaths at each dose level:** See Table 1

Table 1: Deaths at each dose level

| Dosage (mg/kg) | Mortality | | |
|---|---|---|---|
| | Male | Female | Combined |
| 1247 | 0/5 | 0/5 | 0/10 |
| 1484 | 0/5 | 1/5 | 1/10 |
| 1765 | 2/5 | 4/5 | 6/10 |
| 2101 | 3/5 | 4/5 | 7/10 |
| 2500 | 4/5 | 4/5 | 8/10 |

**Remarks:**

- **Time of death:** See Tables 2 - 6
- **Clinical signs at each dose level:** See Tables 2 – 6. Initials signs of reaction to treatment consisted of a rapid progression from reduced motor activity, ataxia, prone posture and prostration to a loss of consciousness between 15 and 30 minutes after administration. Coma and death, between one and six hours after dosing, followed loss of consciousness in a total of 22 animals. The remaining animals generally regained consciousness one to two hours after administration of the lowest dosage, but recovery was less rapid as the dosage increased. All surviving animals were

asymptomatic from Day 3 and all showed normal bodyweight gains over the 14-day observation period.

Table 2: Time of death and clinical signs at 1247 mg/kg dose

| Dosage mg/kg | Signs of reaction to treatment | Animal number and sex | | | | | | | | | | Number showing effect at time after dosing | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | A850 Male | | | | | A851 Female | | | | | Hour | | | | | | Day | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1/4 | 1/2 | 1 | 2 | 4 | 6 | 2 am | 2 pm | 3 | 4 | 5 | 6 | 7 | 8-15 |
| 1247 | **Early decedents** (none) | | | | | | | | | | | | | | | | | | | | | | | | |
| | No. of animals | | | | | | | | | | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | **Animals surviving to Day 15:** | | | | | | | | | | | | | | | | | | | | | | | | |
| | None | | | | | | | | | | | | | | | 4 | 4 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | Piloerection | | | | | + | | + | + | | + | | | 1 | 1 | 2 | 3 | | | | | | | | |
| | Abdominal hunching | | | + | + | | | | | + | | | | 2 | 2 | 1 | | | | | | | | | |
| | Hypoactivity | | + | | + | + | + | + | + | + | + | | | | 3 | 3 | 5 | | | | | | | | |
| | Inactivity | | + | + | + | + | | | | + | | 4 | 3 | 4 | 2 | | | | | | | | | | |
| | Ataxia | | + | + | + | + | | | | + | | 4 | 3 | 4 | 1 | | | | | | | | | | |
| | Unconsciousness | + | | | | | + | + | + | + | + | | 5 | 5 | 3 | 2 | 1 | | | | | | | | |
| | Proneness | | + | + | + | + | | | | | | 4 | 3 | 1 | | | | | | | | | | | |
| | Prostration | + | + | | | | + | + | + | + | + | 6 | 2 | 1 | 2 | 1 | | | | | | | | | |
| | No. of animals | | | | | | | | | | | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |

+ Indicates animal exhibiting sign

Table 3: Time of death and clinical signs at 1484 mg/kg dose

| Dosage mg/kg | Signs of reaction to treatment | Animal number and sex | | | | | | | | | | Number showing effect at time after dosing | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | A852 Male | | | | | A853 Female | | | | | Hour | | | | | | Day | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1/4 | 1/2 | 1 | 2 | 4 | 6 | 2 am | 2 pm | 3 | 4 | 5 | 6 | 7 | 8-15 |
| 1484 | **Early decedents** | | | | | | | | | | | | | | | | | | | | | | | | |
| | Unconsciousness | | | | | | | + | | | | 1 | 1 | 1 | | | | | | | | | | | |
| | Death | | | | | | | + | | | | | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Time of death (hours) | | | | | | | 2 | | | | | | | | | | | | | | | | | |
| | No. of animals | | | | | | | | | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | **Animals surviving to Day 15:** | | | | | | | | | | | | | | | | | | | | | | | | |
| | None | | | | | | | | | | | | | | | | | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | Piloerection | | | + | | + | + | | + | | + | | | | 1 | 4 | 5 | | | | | | | | |
| | Abdominal hunching | | + | | | | | | | | | | 1 | | | 1 | 1 | | | | | | | | |
| | Hypoactivity | | + | + | | + | + | | + | | + | 1 | | | 2 | 3 | 5 | | | | | | | | |
| | Inactivity | | + | + | | + | | | | | | | 1 | 1 | 1 | 2 | | | | | | | | | |
| | Ataxia | | + | | | | + | | + | | + | 1 | 1 | 1 | 2 | | 1 | | | | | | | | |
| | Loss of righting reflex | | | + | | | | | | | | | 1 | | | | | | | | | | | | |
| | Unconsciousness | + | | | + | + | + | | + | + | + | 4 | 7 | 6 | 5 | 4 | 3 | | | | | | | | |
| | Prostration | + | | + | + | + | | | + | | | 4 | 1 | 2 | 1 | | | | | | | | | | |
| | Proneness | | | | | | | | + | | | | | | 1 | | | | | | | | | | |
| | No. of animals | | | | | | | | | | | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |

+ Indicates animal exhibiting sign

Table 4: Time of death and clinical signs at 1764 mg/kg dose

| Dosage mg/kg | Signs of reaction to treatment | Animal number and sex | | | | | | | | | | Number showing effect at time after dosing | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | A854 Male | | | | | A855 Female | | | | | Hour | | | | | | Day | | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1/4 | 1/2 | 1 | 2 | 4 | 6 | 2 | | 3 | 4 | 5 | 6 | 7 | 8-15 |
| | | | | | | | | | | | | | | | | | | am | pm | | | | | | |
| 1765 | **Early decedents** | | | | | | | | | | | | | | | | | | | | | | | | |
| | Unconsciousness | + | | | | + | + | + | + | | + | 6 | 6 | 2 | 1 | 1 | | | | | | | | | |
| | Death | + | | | | + | + | + | + | | + | | | 4 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | Time of death (hours) | 1 | | | | 2 | 6 | 1 | 1 | | 1 | | | | | | | | | | | | | | |
| | No. of animals | | | | | | | | | | | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | **Animals surviving to Day 15:** | | | | | | | | | | | | | | | | | | | | | | | | |
| | None | | | | | | | | | | | | | | 1 | 1 | 1 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| | Hypoactivity | | | + | | | | | | | | | | 1 | | | | | | | | | | | |
| | Inactivity | | | + | | | | | | | | 1 | 1 | | | | | | | | | | | | |
| | Ataxia | | | + | | | | | | | | 1 | 1 | 1 | | | | | | | | | | | |
| | Unconsciousness | | + | | + | | | | | + | | 3 | 3 | 3 | 3 | 3 | 2 | | | | | | | | |
| | Proneness | | | + | | | | | | | | 1 | 1 | | | | 1 | | | | | | | | |
| | Prostration | | | | + | | | | | | | | | | | | | | | | | | | | |
| | Hypopnoea | | + | | | | | | | | | | | 1 | | | | | | | | | | | |
| | No. of animals | | | | | | | | | | | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

+ Indicates animal exhibiting sign

Table 5: Time of death and clinical signs at 2101 mg/kg dose

| Dosage mg/kg | Signs of reaction to treatment | Animal number and sex | | | | | | | | | | Number showing effect at time after dosing | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | A856 Male | | | | | A857 Female | | | | | Hour | | | | | | Day | | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1/4 | 1/2 | 1 | 2 | 4 | 6 | 2 | | 3 | 4 | 5 | 6 | 7 | 8-15 |
| | | | | | | | | | | | | | | | | | | am | pm | | | | | | |
| 2101 | **Early decedents** | | | | | | | | | | | | | | | | | | | | | | | | |
| | Unconsciousness | + | + | | | + | + | + | + | + | | 7 | 7 | 6 | 2 | | | | | | | | | | |
| | Death | + | + | | | + | + | + | + | + | | | | 1 | 5 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | Time of death (hours) | 2 | 1 | | | 4 | 2 | 2 | 4 | 2 | | | | | | | | | | | | | | | |
| | No. of animals | | | | | | | | | | | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| | **Animals surviving to Day 15:** | | | | | | | | | | | | | | | | | | | | | | | | |
| | None | | | | | | | | | | | | | | | | | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 3 |
| | Piloerection | | | + | + | | | | | | + | | | | | | 2 | 1 | | | | | | | |
| | Abdominal hunching | | | | | | | | | | + | | | | | | 1 | | | | | | | | |
| | Hypoactivity | | | + | + | | | | | | + | | | | | | 2 | 2 | 2 | | | | | | |
| | Unconsciousness | | | + | + | | | | | | + | 3 | 3 | 3 | 3 | 3 | 2 | | | | | | | | |
| | Staining about the muzzle | | | + | | | | | | | | | | | | | | | 1 | | | | | | |
| | Ataxia | | | | + | | | | | | + | | | | | | 2 | | | | | | | | |
| | No. of animals | | | | | | | | | | | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

+ Indicates animal exhibiting sign

Table 6: Time of death and clinical signs at 2500 mg/kg dose

| Dosage mg/kg | Signs of reaction to treatment | Animal number and sex | | | | | | | | | | Number showing effect at time after dosing | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | A858 Male | | | | | A859 Female | | | | | Hour | | | | | | Day | | | | | | | | |
| | | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1/4 | 1/2 | 1 | 2 | 4 | 6 | 2 | | 3 | 4 | 5 | 6 | 7 | 8-15 |
| | | | | | | | | | | | | | | | | | | am | pm | | | | | | |
| 2500 | **Early decedents** | | | | | | | | | | | | | | | | | | | | | | | | |
| | Unconsciousness | + | + | + | + | | + | + | + | + | | 8 | 8 | 2 | | | | | | | | | | | |
| | Hypopnea | | | + | | | | | | | | 1 | 1 | | | | | | | | | | | | |
| | Death | + | + | + | + | | + | + | + | + | | | | 6 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | Time of death (hours) | 1 | 1 | 1 | 1 | | 1 | 2 | 2 | 1 | | | | | | | | | | | | | | | |
| | No. of animals | | | | | | | | | | | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | **Animals surviving to Day 15:** | | | | | | | | | | | | | | | | | | | | | | | | |
| | None | | | | | | | | | | | | | | | | | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| | Unconsciousness | | | | | + | | | | | + | 2 | 2 | 2 | 2 | 2 | 2 | | | | | | | | |
| | Dyspnoea | | | | | + | | | | | + | | | | | | 2 | | | | | | | | |
| | Hypopnea | | | | | + | | | | | | 1 | 1 | 1 | 1 | 1 | | | | | | | | | |
| | No. of animals | | | | | | | | | | | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |

+ Indicates animal exhibiting sign

- **Necropsy findings:** See Table 7. Necropsy of early decedents invariably revealed fluid or mucoid dilatation of the gastro-intestinal tract, which was attributed to irritation. Necropsy of animals that survived the observation period revealed no consistent treatment-related effects.

Table 7: Findings at necrospy

| Observation | Incidence of animals with specified pathological changes | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Early decendents | | | | | | | | | | Animals surviving to Day 15 | | | | | | | | | |
| | Dosage (mg/kg) administered to males | | | | | Dosage (mg/kg) administered to females | | | | | Dosage (mg/kg) administered to males | | | | | Dosage (mg/kg) administered to females | | | | |
| | 1247 | 1484 | 1765 | 2101 | 2500 | 1247 | 1484 | 1765 | 2101 | 2500 | 1247 | 1484 | 1765 | 2101 | 2500 | 1247 | 1484 | 1765 | 2101 | 2500 |
| **External** | | | | | | | | | | | | | | | | | | | | |
| NSL | | | 2 | 2 | 3 | | 1 | | 2 | 4 | 5 | 5 | 3 | 2 | 1 | 5 | 4 | | 1 | 1 |
| Muzzle staining | | | | | 1 | | | 1 | 2 | | | | | | | | | | | |
| Suprascapular hair loss | | | | 1 | | | | | | | | | | | | | | | | |
| **Internal** | | | | | | | | | | | | | | | | | | | | |
| NSL | | | | | | | | | | | 5 | 3 | 3 | 2 | 1 | 2 | 4 | 1 | | 1 |
| Lung – areas of congestion on all lobes | | | | | | | | 1 | | | | 2 | | | | | | | 1 | |
| Stomach contents – fluid | | | 2 | 1 | 3 | | | 3 | 3 | 3 | | | | | | | | | | |
| granular | | | | 1 | | | | 1 | | | | | | | | | | | | |
| soft brown material | | | | | | | 1 | | | | | | | | | | | | | |
| Mucosal congestion in pylorus | | | | | 1 | | | | | | | | | | | | | | | |
| Duodenum contents – fluid | | | | | | | | | | 4 | | | | | | | | | | |
| mucoid | | | 2 | 3 | 4 | | 1 | 4 | 4 | 3 | | | | | | | | | | |
| Jejunum contents - fluid | | | | | 2 | | | | | 2 | | | | | | | | | | |
| mucoid | | | 2 | 3 | | | 1 | 4 | 4 | 1 | | | | | | 2 | | | | |
| tympanic | | | | | | | | 1 | | | | | | | | | | | | |
| Ileum contents – mucoid | | | 1 | 1 | 2 | | | 1 | 1 | 2 | | | | | | | | | | |
| Caecum contents – mucoid | | | | | 1 | | | | | | | | | | | | | | | |
| Cannibalised end of tail | | | | | | | | | | | | | | | | 1 | | | | |
| Number of animals examined | 0 | 0 | 2 | 3 | 4 | 0 | 1 | 4 | 4 | 4 | 5 | 5 | 3 | 2 | 1 | 5 | 4 | 1 | 1 | 1 |

NSL No significant lesion

**CONCLUSIONS**

**Remarks:**

**DATA QUALITY**

- **Reliabilities:** 1, Reliable without restriction

**Remarks:** Well conducted study, similar to OECD giudelines

**REFERENCES**

Life Science Research, Dynol: Acute oral toxicity in the rat, Report No. 79/DSB002/565, December 1979

**OTHER**

- **Last Changed:** October 3, 2002
- **Order number for sorting:** 2

**Remarks:**

**HUMAN HEALTH ENDPOINTS (NON SIDS)**
**13.3 SKIN IRRITATION**

## TEST SUBSTANCE

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dead Sea Bromine Company Ltd

## METHOD

- **Method:** U.S. Federal Register, §191.11, 1964
- **Species/strain:** Rabbit, New Zealand White
- **Concentration:** 0.5 g
- **No of animals:** 6
- **Vehicle:** Slightly moistened with distilled water
- **GLP:** No
- **Year:** 1979

**Remarks:** Dynol was used as supplied, slightly moistened with distilled water for easier adherence. Intact and abraded rabbit skin was tested. Occlusive dressing was used.

## RESULTS

- Mildly irritating

**Remarks:** Upon single dermal application a barely discernible erythematous response on the abraded skin of one animal at 72 hours accounted for a Primary Irritation Index of zero. Bandage burn was recognised on 3 animals and slight exfoliation was present in one animal on day 8.

## CONCLUSIONS

**Remarks:** A single dermal application of test substance produced a Primary Irritation Index of zero, thus placing the material into the lowest available class of 'mildly irritating' to the skin.

## REFERENCES (Free Text)

Life Science Research, Dynol: Irritance to rabbit skin (US Federal Register, 1964), Report No. 79/DSB002/440, September 1979

## OTHER

- Last Changed: October 3 2002
- Order number for sorting: 1

**Remarks:** None

**HUMAN HEALTH ENDPOINTS (NON SIDS)**
**13.4 EYE IRRITATION**

## TEST SUBSTANCE

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dead Sea Bromine Company Ltd

## METHOD

- **Method:** U.S. Federal Register, §191.12, 1964
- **Species/strain:** Rabbit, New Zealand White
- **Concentration:** 100 mg
- **No of animals:** 6
- **Vehicle:** none
- **GLP:** No
- **Year:** 1979

**Remarks:** Dynol was used as supplied. 100 mg portions of the test material was placed in the right eye of each test animal. Ocular reaction to treatment was assessed at 24, 48 and 72 hours and seven days after installation. Scoring was carried out using the Draize system.

## RESULTS

- Irritant

**Remarks:** Diffuse corneal opacity affecting less than a quarter of the corneal surface was exhibited by four of the test animals at the 24, 48 and 72-hour post-installation reading. One animal displayed diffuse crimson redness of the conjunctivae in addition to the corneal lesions. All animals exhibited slight conjunctivitis at the 24, 48 and 72-hour readings. This persisted to day 8 in 2 animals. Immediate pain responses upon instillation of the test material ranged from practically no initial pain to moderate initial pain.

## CONCLUSIONS

**Remarks:** A single installation of 100 mg of test substance into the conjunctival sac of six New Zealand White rabbits provoked corneal and conjunctival lesions in four animals regarded as positive reactions under this method. Therefore the test substance was considered to elicit a positive result as an eye irritant. The positive reactions had resolved by Day 8 and may therefore be considered as reversible.

## REFERENCES (Free Text)

Life Science Research, Dynol: Irritance to the rabbit eye (US Federal Register, 1964), Report No. 79/DSB/003/439, September 1979

## OTHER

- Last Changed: October 3 2002
- Order number for sorting: 1

**Remarks:** None

**HUMAN HEALTH ENDPOINTS**
**14.1 GENETIC TOXICITY IN VIVO**

## TEST SUBSTANCE

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dow Chemical Company, Lot No.: 840429-162, Purity: approximately 78.6%, Identity of impurities: 2,2-bis (hydroxymethyl)-1-bromo-3-hydroxypropane (6.6%), 2,2-bis (bromomethyl)-1-bromo-3-hydroxypropane (6.9%), pentaerythritol (0.2%), dimers and structural isomers (7.7%).

## METHOD

- **Method/guideline:** Environmental Health Research & Testing, Inc. method. 3-dose gavage protocol with the test substance administered at 24-hour intervals followed by bone marrow sampling 24 hours after third dosing.
- **Type:** Mouse Micronucleus test
- **GLP:** Yes
- **Year:** 1996
- **Species:** Mice
- **Strain:** B6C3$F_1$
- **Sex:** Male
- **Route of administration:** Oral, gavage
- **Doses/concentration levels:** 100, 200, 300, 400 mg/kg bw
- **Exposure period:** 4 days
- **Statistical methods:** Frequency of micronucleated cells among PCEs analyzed using a one-tailed trend test across dose groups and a t-test for pairwise comparisons of each dose group to the concurrent control.

## Remarks:

- **Age at study initiation:** No data
- **No. of animals per dose:** 5
- **Vehicle:** Corn oil
- **Duration of test:** 4 days
- **Frequency of treatment:** Once every 24 hours for 3 doses
- **Sampling times and number of samples:** Sampled 24 hours after final dose
- **Control groups:** Solvent control: Corn oil;
  Positive control: Injection of 12.5 mg dimethylbenzanthracene per kg bw.
- **Clinical observations performed:** none
- **Organs examined at necropsy:** none
- **Criteria for evaluating results:** 2000 polychromatic erythrocytes scored for frequency of micronucleated cells (5 animals per dose group).
- **Criteria for selection of M.T.D.:** Dose levels were selected after a 13-week repeat dose toxicity study.

## RESULTS

- **Effect on mitotic index or PCE/NCE ratio by dose level by sex:** No data
- **Genotoxic effects:** None in first trial, but there was a clear dose-related increase in micronucleated PCEs in the second trial.

- **NOAEL (NOEL)(C)/LOAEL(LOEL)(C):** No data
- **Statistical results, as appropriate:**

**Remarks:**

- **Mortality at each dose level by sex:** 3 mice died in the first experiment at 400 mg/kg
- **Frequency of Micronuclei:**

| Dose (mg/kg) | Micronucleated Cells/1000 PCEs [a] | |
|---|---|---|
| | Trial 1 - Negative | Trial 2 – Positive |
| Positive control (12.5 mg/kg) | 4.6±1.1 | 7.8±1.3 |
| Solvent control | 1.4±0.6 | 1.5±0.5 |
| 100 | 0.7±0.4 | 2.3±0.3 |
| 200 | 2.5±0.5 | 2.6±0.7 |
| 300 | 2.0±0.7 | |
| 400 [b] | 1.2±1.2 | 4.8±1.2* |
| | P=0.220 [c] | P=0.000 |

* Significantly different (P<0.008) from control

[a] data presented as mean ± standard error; PCE = polychromatic erythrocyte

[b] Only 2 mice survived this group in Trial 1

[c] Trend Test

- **Description, severity, time of onset and duration of clinical signs at each dose level and sex:** no data
- **Bodyweight changes by dose and sex:** No data
- **Food/water consumption by dose and sex:** No data

## CONCLUSIONS

**Remarks:** Results of the first trial were negative. In the second trial, however, there was a clear dose-related increase in micronucleated PCEs. Because the positive response was not reproduced the results were concluded to be equivocal.

## DATA QUALITY

- Reliabilities: 2, Reliable with restrictions

**Remarks:**

## REFERENCES (Free Text)

NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,2-bis(bromomethyl)-1,3-propanediol (FR-1138, CAS No. 3296-90-0) in F344/N Rats and B6C3F1 Mice (Feed Studies), NTP TR 452, National Toxicology Program, May 1996

## OTHER

- **Last Changed:** October 3 2002
- **Order number for sorting:** 1

**Remarks:**

**HUMAN HEALTH ENDPOINTS**
**14.2 GENETIC TOXICITY IN VIVO**

## TEST SUBSTANCE

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dow Chemical Company, Lot No.: 840429-162, Purity: approximately 78.6%, Identity of impurities: 2,2-bis (hydroxymethyl)-1-bromo-3-hydroxypropane (6.6%), 2,2-bis (bromomethyl)-1-bromo-3-hydroxypropane (6.9%), pentaerythritol (0.2%), dimers and structural isomers (7.7%).

## METHOD

- **Method/guideline:** Environmental Health Research & Testing, Inc. method. Single intraperitoneal injection followed by bone marrow sampling 48 hours after dosing.
- **Type:** Mouse Micronucleus test
- **GLP:** Yes
- **Year:** 1996
- **Species:** Mice
- **Strain:** B6C3$F_1$
- **Sex:** Male/Female
- **Route of administration:** Intraperitoneal injection
- **Doses/concentration levels:** 150, 300, 600 mg/kg bw
- **Exposure period:** 2 days
- **Statistical methods:** Data analyzed by the Cochran-Armitage trend test and pairwise comparison of dose groups to the corresponding negative controls were made using a t-test.

**Remarks:**

- **Age at study initiation:** No data
- **No. of animals per dose:** 3 or 4
- **Vehicle:** Corn oil
- **Duration of test:** 2 days
- **Frequency of treatment:** Single dose
- **Sampling times and number of samples:** Sampled 48 hours after dosing
- **Control groups:** Solvent control: Corn oil;
  Positive control: Injection of 200 mg/kg urethane.
- **Clinical observations performed:** none
- **Organs examined at necropsy:** none
- **Criteria for evaluating results:** 1000 polychromatic erythrocytes scored for frequency of micronucleated cells.
- **Criteria for selection of M.T.D.:** Dose levels were selected after a 13-week repeat dose toxicity study and oral bone marrow micronucleus study.

## RESULTS

- **Effect on mitotic index or PCE/NCE ratio by dose level by sex:** No data
- **Genotoxic effects:** Male mice in all three dose groups showed a 2-fold increase in the frequency of micronucleated PCEs. Trend test was not significant due to the similarity in responses and pairwise analyses were also not significant. Female response was stronger

(2.5-fold increase over controls at highest dose) and was directly related to increasing doses of test substance

- **NOAEL (NOEL)(C)/LOAEL(LOEL)(C):** No data
- **Statistical results, as appropriate:**

**Remarks:**

- **Mortality at each dose level by sex:** No deaths reported
- **Frequency of Micronuclei:**

| Dose (mg/kg) | Micronucleated Cells/1000 PCEs [a] | |
|---|---|---|
| | Male | Female |
| Positive control (200 mg/kg) | 16.4±2.2 (3) [b] | 12.1±0.9 (4) |
| Solvent control | 1.5±0.3 (4) | 2.0±0.4 (4) |
| 150 | 3.2±0.8* (4) | 2.7±1.1 (4) |
| 300 | 3.0±0.7* (4) | 3.6±0.9* (3) |
| 600 | 3.0±1.0* (3) | 5.2±0.5* (4) |
| | P=0.150 [c] | P=0.003 |

* Significantly different (P<0.008) from control

[a] Data presented as mean ± standard error; PCE = polychromatic erythrocyte

[b] Number of mice in parentheses

[c] Trend Test

- **Description, severity, time of onset and duration of clinical signs at each dose level and sex:** no data
- **Bodyweight changes by dose and sex:** No data
- **Food/water consumption by dose and sex:** No data

**CONCLUSIONS**

**Remarks:** The results of this experiment provide evidence of the ability of the test substance to induce micronuclei in bone marrow cells of female mice. The results were consistent with the stronger response observed in female mice in the 13-week feed study.

**DATA QUALITY**

- Reliabilities: 2, Reliable with restrictions

**Remarks:**

**REFERENCES (Free Text)**

NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,2-bis(bromomethyl)-1,3-propanediol (FR-1138, CAS No. 3296-90-0) in F344/N Rats and B6C3F1 Mice (Feed Studies), NTP TR 452, National Toxicology Program, May 1996

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 2

**Remarks:**

**HUMAN HEALTH ENDPOINTS**
**14.3 GENETIC TOXICITY IN VIVO**

## TEST SUBSTANCE

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dow Chemical Company, Lot No.: 840429-162, Purity: approximately 78.6%, Identity of impurities: 2,2-bis (hydroxymethyl)-1-bromo-3-hydroxypropane (6.6%), 2,2-bis (bromomethyl)-1-bromo-3-hydroxypropane (6.9%), pentaerythritol (0.2%), dimers and structural isomers (7.7%).

## METHOD

- **Method/guideline:** MacGregor, et al (1990). Blood samples were obtained from animals at the end of the 13 week repeat oral dose toxicity study.
- **Type:** Mouse Peripheral Blood Micronucleus test
- **GLP:** Yes
- **Year:** 1996
- **Species:** Mice
- **Strain:** B6C3$F_1$
- **Sex:** Male/Female
- **Route of administration:** Oral
- **Doses/concentration levels:** 0, 625, 1250, 2500, 5000, 10000 mg/kg bw
- **Exposure period:** 13 weeks
- **Statistical methods:** Log transformation of NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was analyzed by analysis of variance using the SAS GLM procedure. The NCE data for each dose group were compared with the concurrent solvent control using a Student's t-test.

**Remarks:**

- **Age at study initiation:** 6 weeks
- **No. of animals per dose:** 7-10
- **Vehicle:** Feed
- **Duration of test:** 13 weeks
- **Frequency of treatment:** Continuous, ad libitum
- **Sampling times and number of samples:** 1 sample taken at end of study
- **Control groups:** Feed control
- **Clinical observations performed:** none
- **Organs examined at necropsy:** none
- **Criteria for evaluating results:** 10000 normochromatic erythrocytes scored for frequency of micronucleated cells.
- **Criteria for selection of M.T.D.:**

## RESULTS

- **Effect on mitotic index or PCE/NCE ratio by dose level by sex:** No data
- **Genotoxic effects:** Significant increases in micronucleated normochromatic erythrocytes were observed in the 2 highest dose groups of male mice (5000 and 10000 ppm) and the 3 highest dose groups of female mice (2500 to 10000 ppm).

- **NOEL:** 625 ppm (males, not achieved for females)
- **LOEL:** 1250 ppm (males), 625 ppm (females)
- **Statistical results, as appropriate:**

**Remarks:**

- **Mortality at each dose level by sex:** one female (control), 2 males & 1 female (625 ppm), 1 female (1250 ppm), 1 female (2500 ppm), 1 female (5000 ppm), 3 males (10000 ppm) died during the study.

- **Frequency of Micronuclei:**

| Dose (ppm) | Micronucleated NCEs/1000 Cells [a] | |
|---|---|---|
| | Male | Female |
| 0 | 2.36±0.17 (10) [b] | 1.46±0.26 (9) |
| 625 | 2.28±0.29 (8) | 1.86±0.30 (9) |
| 1250 | 2.55±0.18 (10) | 1.86±0.22 (9) |
| 2500 | 2.98±0.21 (10) | 2.72±0.32 [c] (9) |
| 5000 | 3.80±0.19[c] (10) | 4.26±0.47 [c] (9) |
| 10000 | 9.30±1.26 [c] | 11.81±0.54 [c] (9) |
| | P<0.001 [d] | P<0.001 |

[a] Data presented as mean ± standard error; NCE = normochromatic erythrocyte

[b] Number of mice in parentheses

[c] Significant response by pairwise comparison to control

[d] Trend test

- **Description, severity, time of onset and duration of clinical signs at each dose level and sex:** Clinical findings included abnormal posture and hypoactivity in 10000-ppm male and female mice.

- **Bodyweight changes by dose and sex:** The final mean body weights and body weight gains of males and females receiving 1250, 2500, 5000 or 10000-ppm and of females receiving 625 ppm were significantly lower than those of the controls.

- **Food/water consumption by dose and sex:** Feed consumption by exposed mice was generally higher than that by controls throughout the study.

**CONCLUSIONS**

**Remarks:** The test substance was shown to be genotoxic in vivo

**DATA QUALITY**

- Reliabilities: 2, Reliable with restrictions

**Remarks:**

**REFERENCES (Free Text)**

NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,2-bis(bromomethyl)-1,3-propanediol (FR-1138, CAS No. 3296-90-0) in F344/N Rats and B6C3F1 Mice (Feed Studies), NTP TR 452, National Toxicology Program, May 1996

MacGregor, J.T., et al, The in vivo erythrocyte micronucleus test: Measurement at steady state increases assay efficiency and permits integration with toxicity studies. Fundam. Appl. Toxicol., 14, 513-522, 1990

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 3

**Remarks:**

## HUMAN HEALTH ENDPOINTS
## 15.1 GENETIC TOXICITY IN VITRO

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Bromine Compounds Ltd.
Substance: FR-522 Purified (2,2-bis(bromomethyl)-1,3-propanediol), Purity: 99.5%, Lot No.: 616-521-11

**METHOD**

- **Method:** OECD 471, 92/69/EEC Method B14, US EPA, Method: HG-Gene Muta– S. typhimurium: The Salmonella typhimurium reverse mutation assay, 1984
- **Test Type:** Reverse Mutation Assay
- **System of testing:** Bacterial
- **GLP:** Yes
- **Year:** 1995
- **Species/Strain:** Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537
- **Metabolic activation:** S9-mix, Rat liver cells, Aroclor induced
  S9-mix, Hamster liver cells, uninduced
- **Concentrations tested:** 50, 150, 500, 1500, 5000 µg/plate
- **Statistical Methods:** None

**Remarks:**

- **Test Design**

  - **Number of replicates:** 3
  - **Positive Controls:** N-ethyl-N'-nitroso-N-nitrosoguanidine (TA100, TA1535, -S9)
    9-aminoacridine (TA1537, -S9)
    2-nitrofluorene (TA98, -S9)
    2-aminoanthracene (TA98, TA100, TA 1535, TA1537, +S9)
    Congo red (TA98, +S9)
  - **Negative Control:** Solvent vehicle

- **Solvent:** Dimethylsulfoxide

**RESULTS**

- **Result:** Positive
- **Cytotoxic concentration**

  - **With metabolic activation:** > 5000 µg/plate
  - **Without metabolic activation:** > 5000 µg/plate

- **Genotoxic effects**
  - **With metabolic activation:** Large dose-related increases in revertant colony numbers were observed with strain TA1535. These increases were observed only in the presence of hamster S-9

mix and were largest in the presence of the 30% mix. A smaller increase was also observed with strain TA100 in the presence of 30% hamster S-9 mix.

- **Without metabolic activation:** None

- **Statistical results:**

| Strain | Dose level (µg/plate) | Revertants/Plate [a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Test 1 | | | | Test 2 | | | |
| | | -S9 | +10% Rat S9 | +10% Hamster S9 | +30% Hamster S9 | -S9 | +10% Rat S9 | +10% Hamster S9 | +30% Hamster S9 |
| TA1535 | 5000 | 17±4.0 | 17±1.7 | 67±14.6 | 243±28.8 | 16±3.6 | 15±3.0 | 85±20.0 | 217±15 |
| | 1500 | 15±5.5 | 11±1.0 | 27±0.6 | 90±4.5 | 15±2.1 | 15±4.0 | 35±5.3 | 92±5.7 |
| | 500 | 12±4.5 | 14±5.8 | 17±4.6 | 52±21.9 | 17±4.6 | 13±4.6 | 21±5.5 | 71±0.6 |
| | 150 | 16±2.5 | 12±2.3 | 17±5.0 | 24±5.5 | 13±4.0 | 12±3.6 | 20±6.1 | 37±6.4 |
| | 50 | 16±6.1 | 15±3.6 | 15±3.6 | 22±5.1 | 17±1.2 | 12±0.0 | 18±2.3 | 18±5.6 |
| | 0 | 13±1.2 | 14±4.5 | 15±4.5 | 15±3.2 | 15±1.5 | 13±3.1 | 15±4.9 | 13±3.8 |
| | Solvent | 18±5.5 | 12±1.7 | 16±5.2 | 15±3.6 | 15±4.5 | 19±3.2 | 16±3.1 | 17±0.7 |
| | ENNG (5.0) | 1361±20.1 | | | | 1485±16.8 | | | |
| | AA (2.0) | | 88±14.2 | 157±4.7 | 137±18.6 | | 185±5.3 | 202±18.0 | 203±16.8 |
| TA1537 | 5000 | 7±0.6 | 6±2.3 | 8±3.5 | 13±2.1 | 14±3.6 | 11±2.0 | 10±4.2 | 12±3.1 |
| | 1500 | 9±3.2 | 8±3.6 | 11±1.0 | 11±3.5 | 14±2.0 | 10±4.2 | 16±1.5 | 11±3.2 |
| | 500 | 6±0.0 | 7±4.7 | 10±2.6 | 10±5.1 | 16±2.6 | 11±1.0 | 11±2.6 | 11±2.9 |
| | 150 | 5±1.7 | 9±2.5 | 10±3.1 | 10±2.9 | 11±2.5 | 12±4.0 | 13±2.1 | 11±4.0 |
| | 50 | 8±3.2 | 11±1.2 | 10±3.5 | 10±2.5 | 15±4.7 | 12±3.6 | 15±2.0 | 11±2.6 |
| | 0 | 8±1.7 | 14±2.6 | 9±3.1 | 13±1.5 | 8±3.0 | 9±1.0 | 13±4.0 | 11±2.6 |
| | Solvent | 10±0.6 | 12±3.8 | 12±1.7 | 11±2.1 | 11±5.0 | 14±1.7 | 11±1.2 | 12±1.5 |
| | 9 AC (80.8) | X | | | | X | | | |
| | AA (2.0) | | 67±15.5 | 459±22.5 | 383±25.1 | | 163±15.3 | 235±51.9 | 257±38.2 |
| TA98 | 5000 | 21±2.0 | 26±4.7 | 31±2.6 | 28±5.1 | 27±0.0 | 28±6.4 | 24±1.7 | 29±4.0 |
| | 1500 | 21±1.5 | 26±3.8 | 23±3.6 | 26±5.5 | 28±5.5 | 26±4.9 | 26±4.0 | 29±0.6 |
| | 500 | 20±3.6 | 26±3.5 | 25±3.8 | 26±3.5 | 25±5.0 | 24±3.8 | 28±4.2 | 22±3.5 |
| | 150 | 22±3.8 | 31±2.9 | 26±2.5 | 25±1.7 | 21±1.2 | 27±1.5 | 25±1.7 | 26±4.0 |
| | 50 | 18±4.0 | 25±6.0 | 24±4.0 | 27±2.6 | 27±2.5 | 28±1.0 | 22±2.6 | 24±4.2 |
| | 0 | 24±1.5 | 28±1.5 | 23±2.3 | 26±4.6 | 22±0.6 | 25±4.7 | 26±4.5 | 28±3.1 |
| | Solvent | 23±0.6 | 29±2.1 | 23±3.2 | 25±2.1 | 24±2.1 | 25±6.4 | 25±4.4 | 27±0.0 |
| | NF (1.0) | 338±7.0 | | | | 275±6.2 | | | |
| | AA (0.5) | | 152±16.8 | 122±64.4 | 167±26.8 | | 232±19.3 | 237±17.3 | 194±9.2 |
| | CR (200.0) | | 20±2.5 | 34±11.5 | 105±13.6 | | 43±9.6 | 64±6.2 | 218±17.4 |
| TA100 | 5000 | 116±4.2 | 125±8.2 | 136±19.1 | 271±28.0 | 122±5.7 | 122±11.8 | 138±26.2 | 242±46.4 |
| | 1500 | 130±4.2 | 130±7.8 | 148±17.8 | 175±7.0 | 120±3.6 | 119±11.0 | 136±6.7 | 201±6.6 |
| | 500 | 116±8.6 | 134±7.5 | 143±2.6 | 140±11.3 | 132±11.6 | 119±5.8 | 138±10.7 | 176±12.7 |
| | 150 | 130±5.0 | 122±2.0 | 127±2.6 | 141±7.0 | 124±10.4 | 133±12.3 | 128±13.1 | 175±20.0 |
| | 50 | 130±3.6 | 119±14.9 | 124±11.9 | 152±11.1 | 109±5.1 | 138±18.7 | 128±17.0 | 128±6.1 |
| | 0 | 125±8.1 | 140±13.1 | 144±13.8 | 150±5.6 | 122±17.1 | 127±14.5 | 137±15.9 | 136±11.5 |
| | Solvent | 124±2.3 | 118±13.0 | 119±8.7 | 143±11.5 | 115±11.1 | 123±15.9 | 143±3.5 | 137±18.9 |
| | ENNG (3.0) | 654±50.3 | | | | 1568±52.8 | | | |
| | AA (1.0) | | 460±3.6 | 886±21.6 | 485±123.8 | | 444±24.1 | 723±41.6 | 650±121.3 |

[a] Data presented as mean ± standard deviation

ENNG N-ethyl-N'-nitro-N-nitrosoguanidine, 9 AC 9-aminoacridine, NF 2-nitrofluorene, AA 2-aminoanthracene, CR Congo red

X Too many colonies to count accurately

**Remarks:** None

**CONCLUSIONS**

**Remarks:** It is concluded that, when tested in dimethylsulfoxide, the test substance shows no evidence of mutagenic activity in the absence or presence of rat S-9 mix. The test substance shows clear evidence of mutagenic activity with strains TA1535 and TA100 in the presence of hamster S-9 mix.

**DATA QUALITY**

- **Reliabilities:** 1, Reliable without restrictions

**Remarks:** Study conducted under GLP to OECD/EC/EPA test guidelines by Huntingdon Life Sciences.

**REFERENCES**

Huntingdon Life Sciences Ltd., FR-522 Purified, Bacterial Mutation Assay, February 1996

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 1

**Remarks:** S-9 is usually only prepared from a rat previously treated with a compound (Aroclor) known to induce a high level of enzymic activity. However in this study S-9 mix using liver fraction from uninduced Syrian hamsters was also used as it was suspected that the test substance may be metabolised to a mutagen by hamster S-9 but not by rat.

## HUMAN HEALTH ENDPOINTS
## 15.2 GENETIC TOXICITY IN VITRO

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Bromine Compounds Ltd.
Substance: FR -522 (2,2-bis(bromomethyl)-1,3-propanediol), Purity: 98.63%, Lot No.: 953038

**METHOD**

- **Method:** OECD 471, 92/69/EEC Method B14, US EPA, Method: HG-Gene Muta – S. typhimurium: The Salmonella typhimurium reverse mutation assay, 1984
- **Test Type:** Reverse Mutation Assay
- **System of testing:** Bacterial
- **GLP:** Yes
- **Year:** 1996
- **Species/Strain:** Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537
- **Metabolic activation:** S9-mix, Rat liver cells, Aroclor induced
  S9-mix, Hamster liver cells, uninduced
- **Concentrations tested:** 50, 150, 500, 1500, 5000 µg/plate
- **Statistical Methods:** None

**Remarks:**

- **Test Design**

  - **Number of replicates:** 3
  - **Positive Controls:** N-ethyl-N'-nitroso-N-nitrosoguanidine (TA100, TA1535, -S9)
    9-aminoacridine (TA1537, -S9)
    2-nitrofluorene (TA98, -S9)
    2-aminoanthracene (TA98, TA100, TA 1535, TA1537, +S9)
    Congo red (TA98, +S9)
  - **Negative Control:** Solvent vehicle

- **Solvent:** Dimethylsulfoxide

**RESULTS**

- **Result:** Positive
- **Cytotoxic concentration**

  - **With metabolic activation:** > 5000 µg/plate
  - **Without metabolic activation:** > 5000 µg/plate

- **Genotoxic effects**
  - **With metabolic activation:** Fairly large dose-related increases in revertant colony numbers were observed with strains TA1535 and TA 100. These increases were observed only in the presence of hamster S-9 mix and were largest in the presence of the 30% mix.

- **Without metabolic activation:** None

- **Statistical results:**

| Strain | Dose level (µg/plate) | Revertants/Plate [a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Test 1 | | | | Test 2 | | | |
| | | -S9 | +10% Rat S9 | +10% Hamster S9 | +30% Hamster S9 | -S9 | +10% Rat S9 | +10% Hamster S9 | +30% Hamster S9 |
| TA1535 | 5000 | 13±4.9 | 15±4.6 | 46±11.8 | 108±15.9 | 10±4.6 | 11±4.2 | 33±6.0 | 177±16.2 |
| | 1500 | 17±3.1 | 18±3.6 | 53±8.2 | 73±5.9 | 11±4.7 | 12±4.0 | 30±3.6 | 49±17.1 |
| | 500 | 12±2.3 | 17±4.6 | 16±3.1 | 29±13.1 | 13±2.3 | 8±3.5 | 19±11.0 | 37±1.0 |
| | 150 | 11±3.0 | 12±1.5 | 18±2.6 | 29±5.2 | 14±5.5 | 14±4.5 | 17±4.5 | 10±4.0 |
| | 50 | 12±5.3 | 13±3.0 | 11±2.1 | 12±6.7 | 12±3.6 | 16±2.1 | 16±4.6 | 12±2.5 |
| | 0 | 11±0.6 | 15±2.0 | 14±4.6 | 14±5.3 | 8±1.2 | 9±2.5 | 13±5.0 | 11±5.3 |
| | Solvent | 13±3.5 | 16±4.6 | 11±3.5 | 14±3.8 | 10±1.5 | 16±3.8 | 11±3.5 | 11±1.0 |
| | ENNG (5.0) | 1192±83.4 | | | | 1455±49.7 | | | |
| | AA (2.0) | | 77±11.0 | 116±68.5 | 160±5.6 | | 87±13.7 | 91±15.0 | 152±11.0 |
| TA1537 | 5000 | 12±5.6 | 10±6.7 | 14±2.1 | 9±3.1 | 9±0.6 | 8±1.2 | 8±1.2 | 10±1.0 |
| | 1500 | 14±4.2 | 12±4.6 | 11±0.6 | 13±5.3 | 7±1.0 | 7±1.5 | 7±1.5 | 9±3.5 |
| | 500 | 11±3.2 | 12±1.0 | 12±2.6 | 15±2.6 | 9±4.4 | 9±2.1 | 7±6.1 | 10±2.0 |
| | 150 | 15±4.6 | 12±2.1 | 16±3.5 | 13±3.1 | 12±4.7 | 9±4.0 | 11±1.0 | 12±1.5 |
| | 50 | 12±6.4 | 14±3.6 | 15±3.5 | 11±4.9 | 15±4.4 | 14±5.0 | 10±2.1 | 15±1.7 |
| | 0 | 11±1.0 | 11±0.0 | 14±1.2 | 11±2.9 | 9±1.0 | 8±1.2 | 10±4.0 | 8±4.9 |
| | Solvent | 9±1.0 | 13±2.9 | 12±1.2 | 11±3.1 | 8±0.6 | 8±0.6 | 10±3.1 | 9±2.6 |
| | 9 AC (80.0) | X | | | | X | | | |
| | AA (2.0) | | 42±5.8 | 195±12.1 | 160±41.9 | | 71±4.7 | 142±10.8 | 163±25.1 |
| TA98 | 5000 | 22±6.6 | 26±5.9 | 26±5.5 | 26±4.5 | 25±1.7 | 27±1.2 | 22±2.6 | 26±4.0 |
| | 1500 | 27±1.7 | 30±5.7 | 30±6.0 | 31±4.9 | 23±2.6 | 22±3.5 | 24±3.6 | 29±3.2 |
| | 500 | 22±5.6 | 29±5.1 | 23±2.1 | 23±3.5 | 22±4.7 | 27±5.5 | 23±4.6 | 28±4.5 |
| | 150 | 28±3.2 | 30±3.2 | 23±7.0 | 20±4.2 | 22±2.5 | 25±3.2 | 22±0.6 | 25±1.7 |
| | 50 | 26±2.5 | 29±3.5 | 23±4.0 | 33±2.6 | 23±5.3 | 23±5.9 | 26±2.3 | 27±0.6 |
| | 0 | 22±4.0 | 27±4.2 | 22±4.4 | 29±4.7 | 18±2.0 | 22±1.0 | 24±2.1 | 28±3.6 |
| | Solvent | 28±3.1 | 27±4.5 | 26±2.0 | 28±3.2 | 18±1.7 | 25±4.0 | 20±1.0 | 28±4.2 |
| | NF (1.0) | 146±23.4 | | | | 274±8.1 | | | |
| | AA (0.5) | | 101±16.7 | 419±9.3 | 392±82.1 | | 170±30.8 | 376±30.5 | 397±14.5 |
| | CR (200.0) | | 33±3.2 | 39±3.1 | 127±13.3 | | 32±2.3 | 57±1.7 | 181±11.7 |
| TA100 | 5000 | 125±11.8 | 126± - | 159±14.1 | 178±24.3 | 100±8.1 | 121±5.0 | 146±12.8 | 239±50.0 |
| | 1500 | 129±13.7 | 135±2.6 | 137±4.9 | 182±14.4 | 98±22.4 | 113±6.6 | 153±3.5 | 186±1.5 |
| | 500 | 93±3.8 | 115±10.8 | 125±18.5 | 131±12.7 | 110±9.5 | 106±15.6 | 115±6.6 | 134±9.9 |
| | 150 | 98±7.2 | 115±10.1 | 129±8.1 | 148±13.7 | 118±14.6 | 133±10.3 | 140±14.5 | 142±11.2 |
| | 50 | 115±13.4 | 131±15.7 | 119±5.0 | 133±3.6 | 105±7.1 | 112±6.1 | 108±12.9 | 128±8.1 |
| | 0 | 110±16.5 | 112±14.0 | 129±19.3 | 124±12.2 | 116±18.6 | 115±12.5 | 103±14.7 | 128±10.7 |
| | Solvent | 105±3.0 | 110±6.4 | 126±9.3 | 129±7.1 | 101±9.0 | 124±1.0 | 127±13.9 | 123±8.0 |
| | ENNG (3.0) | 825±115.8 | | | | 1426±34.8 | | | |
| | AA (1.0) | | 333±109.3 | 837±146.7 | 613±313.8 | | 324±33.0 | 979±127.3 | 519±122.4 |

[a] Data presented as mean ± standard deviation

ENNG N-ethyl-N'-nitro-N-nitrosoguanidine, 9 AC 9-aminoacridine, NF 2-nitrofluorene, AA 2-aminoanthracene, CR Congo red

X Too many colonies to count accurately

**Remarks:** None

**CONCLUSIONS**

**Remarks:** It is concluded that, when tested in dimethylsulfoxide, the test substance shows no evidence of mutagenic activity in the absence or presence of rat S-9 mix. The test substance shows clear evidence of mutagenic activity with strains TA1535 and TA100 in the presence of hamster S-9 mix.

**DATA QUALITY**

- **Reliabilities:** 1, Reliable without restrictions

**Remarks:** Study conducted under GLP to OECD/EC/EPA test guideline by Huntingdon Life Sciences.

**REFERENCES**

Huntingdon Life Sciences Ltd., FR-522, Bacterial Mutation Assay, January 1996

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 2

**Remarks:** S-9 is usually only prepared from a rat previously treated with a compound (Aroclor) known to induce a high level of enzymic activity. However in this study S-9 mix using liver fraction from uninduced Syrian hamsters was also used as it was suspected that the test substance may be metabolised to a mutagen by hamster S-9 but not by rat.

## HUMAN HEALTH ENDPOINTS
## 15.3 GENETIC TOXICITY IN VITRO

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Bromine Compounds Ltd.
Substance: FR-522C (2,2-bis(bromomethyl)-1,3-propanediol), Purity: 88.4%, Lot No.: 1138

**METHOD**

- **Method:** OECD 471, 92/69/EEC Method B14, U S EPA, Method: HG-Gene Muta – S. typhimurium: The Salmonella typhimurium reverse mutation assay, 1984
- **Test Type:** Reverse Mutation Assay
- **System of testing:** Bacterial
- **GLP:** Yes
- **Year:** 1996
- **Species/Strain:** Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537
- **Metabolic activation:** S9-mix, Rat liver cells, Aroclor induced
  S9-mix, Hamster liver cells, uninduced
- **Concentrations tested:** 50, 150, 500, 1500, 5000 µg/plate
- **Statistical Methods:** None

**Remarks:**

- **Test Design**
  - **Number of replicates:** 3
  - **Positive Controls:** N-ethyl-N'-nitroso-N-nitrosoguanidine (TA100, TA1535, -S9)
    9-aminoacridine (TA1537, -S9)
    2-nitrofluorene (TA98, -S9)
    2-aminoanthracene (TA98, TA100, TA 1535, TA1537, +S9)
    Congo red (TA98, +S9)
  - **Negative Control:** Solvent vehicle
- **Solvent:** Dimethylsulfoxide

**RESULTS**

- **Result:** Positive
- **Cytotoxic concentration**
  - **With metabolic activation:** > 5000 µg/plate
  - **Without metabolic activation:** > 5000 µg/plate
- **Genotoxic effects**
  - **With metabolic activation:** Large dose-related increases in revertant colony numbers were observed with strains TA1535 and TA 100. These increases were observed only in the presence of hamster S-9 mix.
  - **Without metabolic activation:** None

- **Statistical results:**

| Strain | Dose level (µg/plate) | Revertants/Plate [a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Test 1 | | | | Test 2 | | | |
| | | -S9 | +10% Rat S9 | +10% Hamster S9 | +30% Hamster S9 | -S9 | +10% Rat S9 | +10% Hamster S9 | +30% Hamster S9 |
| TA1535 | 5000 | 10±3.5 | 14±2.1 | 97±86 | 250±32.4 | 13±3.2 | 11±3.8 | 46±8.1 | 122±8.5 |
| | 1500 | 15±5.6 | 18±2.6 | 86±14.7 | 179±7.5 | 10±1.0 | 10±3.0 | 39±6.7 | 82±20.8 |
| | 500 | 12±3.0 | 15±2.1 | 57±6.6 | 118±15.1 | 13±1.2 | 14±4.2 | 38±8.5 | 65±28.6 |
| | 150 | 12±3.5 | 12±4.4 | 28±8.5 | 48±11.6 | 13±1.2 | 14±- | 14±6.1 | 38±11.6 |
| | 50 | 8±1.7 | 16±4.4 | 30±9.1 | 31±1.5 | 17±3.2 | 13±3.1 | 17±2.1 | 19±1.5 |
| | 0 | 11±0.6 | 15±2.0 | 14±4.6 | 14±5.3 | 8±1.2 | 9±2.5 | 13±5.0 | 11±5.3 |
| | Solvent | 13±3.5 | 16±4.6 | 11±3.5 | 14±3.8 | 10±1.5 | 16±3.8 | 11±3.5 | 11±1.0 |
| | ENNG (5.0) | 1192±83.4 | | | | 1455±49.7 | | | |
| | AA (2.0) | | 77±11.0 | 116±68.5 | 160±5.6 | | 87±13.7 | 91±15.0 | 152±11.0 |
| TA1537 | 5000 | 9±1.7 | 13±4.2 | 9±3.1 | 12±2.1 | 11±1.7 | 14±7.1 | 14±4.4 | 10±2.5 |
| | 1500 | 10±0.6 | 9±3.5 | 12±4.0 | 9±2.0 | 11±3.6 | 12±4.0 | 10±4.4 | 11±1.0 |
| | 500 | 12±1.7 | 10±3.1 | 14±2.3 | 11±3.5 | 13±4.7 | 10±4.0 | 11±5.5 | 13±4.5 |
| | 150 | 13±2.3 | 8±1.2 | 9±2.5 | 13±5.5 | 9±1.7 | 12±2.9 | 10±4.0 | 13±3.5 |
| | 50 | 13±5.5 | 8±3.2 | 14±2.1 | 16±3.1 | 12±2.5 | 12±2.6 | 14±3.2 | 12±4.2 |
| | 0 | 11±1.0 | 11±0.0 | 14±1.2 | 11±2.9 | 9±1.0 | 8±1.23 | 10±4.0 | 8±4.9 |
| | Solvent | 9±1.0 | 13±2.9 | 12±1.2 | 11±3.1 | 8±0.6 | 8±0.6 | 10±3.1 | 9±2.6 |
| | 9 AC (80.8) | X | | | | X | | | |
| | AA (2.0) | | 42±5.8 | 195±12.1 | 160±41.9 | | 71±4.7 | 142±10.8 | 163±25.1 |
| TA98 | 5000 | 15±5.0 | 24±2.1 | 24±5.6 | 31±1.0 | 20±2.9 | 20±5.7 | 24±7.6 | 26±3.5 |
| | 1500 | 21±5.7 | 31±2.5 | 24±1.0 | 25±7.8 | 20±3.5 | 23±3.2 | 24±2.9 | 25±3.6 |
| | 500 | 19±1.0 | 26±3.6 | 21±4.6 | 30±4.6 | 26±3.2 | 24±5.0 | 22±0.6 | 27±2.6 |
| | 150 | 18±1.2 | 27±5.1 | 27±6.8 | 20±3.6 | 20±2.1 | 28±1.7 | 26±6.5 | 25±7.0 |
| | 50 | 18±1.0 | 23±7.0 | 27±3.5 | 23±5.2 | 27±3.5 | 28±7.1 | 25±0.6 | 22±4.0 |
| | 0 | 22±4.0 | 27±4.2 | 22±4.4 | 29±4.7 | 18±2.0 | 22±1.0 | 24±2.1 | 28±3.6 |
| | Solvent | 28±3.1 | 27±4.5 | 26±2.0 | 28±3.2 | 18±1.7 | 25±4.0 | 20±1.0 | 28±4.2 |
| | NF (1.0) | 146±23.4 | | | | 274±8.1 | | | |
| | AA (0.5) | | 101±16.7 | 419±9.3 | 392±82.1 | | 170±30.8 | 376±30.5 | 397±14.5 |
| | CR (200.0) | | 33±3.2 | 39±3.1 | 127±13.3 | | 32±2.3 | 57±1.7 | 181±11.7 |
| TA100 | 5000 | 123±3.8 | 138±11.7 | 148±12.0 | 244±16.9 | 130±14.5 | 124±4.4 | 138±10.5 | 228±9.8 |
| | 1500 | 105±9.5 | 122±3.5 | 159±18.9 | 200±40.8 | 117±13.7 | 132±16.6 | 179±14.6 | 208±21.5 |
| | 500 | 107±15.5 | 134±6.5 | 142±9.5 | 157±4.0 | 113±10.0 | 123±6.7 | 140±3.2 | 161±9.8 |
| | 150 | 110±6.1 | 120±4.0 | 129±6.5 | 134±6.1 | 108±4.0 | 124±15.9 | 118±9.0 | 146±2.1 |
| | 50 | 115±4.0 | 129±3.6 | 141±8.5 | 138±25.5 | 117±11.0 | 134±5.3 | 130±12.3 | 137±4.7 |
| | 0 | 110±16.5 | 112±14.0 | 129±19.3 | 124±12.2 | 116±18.6 | 115±12.5 | 103±14.8 | 128±10.7 |
| | Solvent | 105±3.0 | 110±6.4 | 126±9.3 | 129±7.1 | 101±9.0 | 124±1.0 | 127±13.9 | 123±8.0 |
| | ENNG (3.0) | 825±115.8 | | | | 1426±34.8 | | | |
| | AA (1.0) | | 333±109.3 | 837±146.7 | 613±313.8 | | 324±33.0 | 979±127.3 | 519±122.4 |

[a] Data presented as mean ± standard deviation

ENNG N-ethyl-N'-nitro-N-nitrosoguanidine, 9 AC 9-aminoacridine, NF 2-nitrofluorene, AA 2-aminoanthracene, CR Congo red

X Too many colonies to count accurately

**Remarks:** None

**CONCLUSIONS**

**Remarks:** It is concluded that, when tested in dimethylsulfoxide, the test substance shows no evidence of mutagenic activity in the absence or presence of rat S-9 mix. The test substance shows clear evidence of mutagenic activity with strains TA1535 and TA100 in the presence of hamster S-9 mix.

**DATA QUALITY**

- **Reliabilities:** 1, Reliable without restrictions

**Remarks:** Study conducted under GLP to OECD/EC/EPA test guidelines by Huntingdon Life Sciences.

**REFERENCES**

Huntingdon Life Sciences Ltd., FR-522C, Bacterial Mutation Assay, January 1996

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 3

**Remarks:** S-9 is usually only prepared from a rat previously treated with a compound (Aroclor) known to induce a high level of enzymic activity. However in this study S-9 mix using liver fraction from uninduced Syrian hamsters was also used as it was suspected that the test substance may be metabolised to a mutagen by hamster S-9 but not by rat.

## HUMAN HEALTH ENDPOINTS
## 15.4 GENETIC TOXICITY IN VITRO

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Radian Corporation

**METHOD**

- **Method:** similar to OECD 471.
- **Test Type:** Reverse Mutation Assay
- **System of testing:** Bacterial
- **GLP:** No data
- **Year:** 1986 (Expt 1, Mortelmans, et al), 1992 (Expt 2, Zeiger, et al)
- **Species/Strain:** Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537
- **Metabolic activation:** S9-mix, Rat liver cells, Aroclor induced
  S9-mix, Hamster liver cells, Aroclor induced
- **Concentrations tested:** Expt 1: 0, 33, 100, 333, 1000, 3333, 10000 µg/plate
  Expt 2: 0, 10, 33, 100, 333, 1000, 1666, 3333, 6666 µg/plate
- **Statistical Methods:** None

**Remarks:**

- **Test Design**

  - **Number of replicates:** 3
  - **Positive Controls:** Sodium azide (TA100, TA1535, -S9)
    9-aminoacridine (TA1537, -S9)
    4-nitro-o-phenylenediamine (TA98, -S9)
    2-aminoanthracene (TA98, TA100, TA 1535, TA1537, +S9)

  - **Negative Control:** Solvent vehicle

- **Solvent:** No data

**RESULTS**

- **Result:** Positive
- **Cytotoxic concentration**

  - **With metabolic activation:** > 10000 µg/plate (Expt 1), > 6666 µg/plate (Expt 2)
  - **Without metabolic activation:** > 10000 µg/plate (Expt 1), > 6666 µg/plate (Expt 2)

- **Genotoxic effects**

  - **With metabolic activation:**
    Experiment 1: Weakly positive with TA100 in the presence of 10% hamster S9 (not reproduced in second test). Negative with 10% rat S9 mix with all strains.

Experiment 2: Positive with TA100 in the presence of 30% hamster S9 mix. Negative with 30% rat S9 mix with all strains.

- **Without metabolic activation:**
  Experiment 1: None
  Experiment 2: none

- **Statistical results:**

Expt 1 (Mortelmans, et al)

| Strain | Dose (µg/plate) | Revertants/Plate [a] -S9 Trial 1 | -S9 Trial 2 | +10% hamster S9 Trial 1 | +10% hamster S9 Trial 2 | +10% rat S9 Trial 1 | +10% rat S9 Trial 2 |
|---|---|---|---|---|---|---|---|
| TA100 | 0 | 69±3.8 | 83±3.5 | 77±4.2 | 94±9.0 | 81±3.2 | 76±4.6 |
| | 10 | | 64±6.0 | | | | |
| | 33 | 76±1.9 | 59±6.0 | | | | |
| | 100 | 64±5.3 | 56±3.5 | 88±6.2 | 105±11.3 | 93±7.3 | 85±4.8 |
| | 333 | 55±5.0 | 61±4.0 | 105±7.5 | 93±4.0 | 85±7.3 | 76±4.8 |
| | 1000 | toxic | 56±2.5 | 112±7.2 | 107±9.5 | 93±1.2 | 79±6.0 |
| | 3333 | toxic | | 126±0.0 | 106±8.5 | 82±6.9 | 85±7.0 |
| | 10000 | | | toxic | 110±10.0 | toxic | 71±8.4 |
| Trial Summary | | Negative | Negative | Weakly Positive | Negative | Negative | Negative |
| Positive Control | | 625±45.2 | 429±44.2 | 1468±2.9 | 1171±157.7 | 1362±92.4 | 1044±44.5 |
| TA1535 | 0 | 6±0.9 | 7±0.7 | 6±0.6 | 10±0.9 | 8±0.3 | 6±2.0 |
| | 10 | | | | | | |
| | 33 | 4±0.9 | 6±0.6 | | | | |
| | 100 | 5±1.9 | 9±1.5 | 10±1.7 | 10±1.3 | 10±2.1 | 10±2.0 |
| | 333 | 2±1.0 | 6±0.6 | 17±2.4 | 14±1.9 | 11±2.2 | 10±1.2 |
| | 1000 | 3±1.2 | 10±1.8 | 14±3.2 | 10±4.5 | 10±0.3 | 10±0.3 |
| | 3333 | 2±0.7 | toxic | 16±3.0 | 16±1.8 | 12±1.7 | 10±0.9 |
| | 10000 | | | 12±1.2 | 14±1.9 | 10±1.8 | 11±0.7 |
| Trial Summary | | Negative | Negative | Equivocal | Negative | Negative | Negative |
| Positive Control | | 471±110.0 | 488±98.5 | 128±3.9 | 113±15.5 | 280±31.9 | 71±11.6 |
| TA1537 | 0 | 2±0.9 | 6±0.6 | 6±1.9 | 10±1.5 | 7±0.9 | 10±1.5 |
| | 33 | 1± 0.3 | 4±1.2 | | | | |
| | 100 | 1±0.6 | 8±0.9 | 5±0.9 | 7±1.2 | 5±1.5 | 6±1.2 |
| | 333 | 0±0.3 | 7±1.8 | 3±0.3 | 7±1.0 | 6±2.1 | 10±1.5 |
| | 1000 | 0±0.0 | 3±2.0 | 6±1.5 | 10±2.1 | 2±0.9 | 9±0.3 |
| | 3333 | 1±0.3 | 3±3.0 | 2±1.0 | 9±1.2 | 2±0.9 | 7±0.6 |
| | 10000 | | | 2±0.9 | toxic | 2±0.6 | 7±1.5 |
| Trial Summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive Control | | 432±12.9 | 55±6.8 | 74±3.5 | 52±7.0 | 58±3.0 | 71±15.8 |
| TA98 | 0 | 21±2.2 | 18±4.0 | 11±0.9 | 21±3.2 | 10±0.6 | 23±1.7 |
| | 10 | | 11±1.5 | | | | |
| | 33 | 9±1.5 | 12±1.2 | | | | |
| | 100 | 12±2.4 | 11±1.2 | 15±1.8 | 14±4.4 | 12±1.2 | 20±0.3 |
| | 333 | 7±1.3 | 12±1.5 | 13±1.8 | 19±4.6 | 12±1.0 | 20±1.2 |
| | 1000 | toxic | 8±0.3 | 10±2.1 | 22±1.2 | 13±3.4 | 19±2.3 |
| | 3333 | toxi c | | 14±0.6 | 23±1.9 | 13±1.2 | 20±3.8 |
| | 10000 | | | 3±0.9 | 19±3.5 | 8±1.2 | 21±1.2 |
| Trial Summary | | Negative | Negative | Negative | Negative | Negative | Negative |
| Positive Control | | 129±18 | 462±34.7 | 1076±45.0 | 854±74.9 | 481±83.0 | 568±8.4 |

[a] Revertants are presented as mean ± standard error from 3 plates

Expt 2 (Zeiger, et al)

| Strain | Dose (µg/plate) | Revertants/Plate [a] -S9 Trial 1 | -S9 Trial 2 | +30% hamster S9 Trial 1 | +30% hamster S9 Trial 2 | +30% rat S9 Trial 1 |
|---|---|---|---|---|---|---|
| TA100 | 0 | 159±3.5 | 161±11.1 | 151±4.7 | 160±10.2 | 170±9.0 |
| | 10 | | 149±11.8 | | | |
| | 33 | | 164±13.5 | | | |
| | 100 | 152±7.0 | 150±10.4 | 156±8.1 | 172±11.5 | 154±10.1 |
| | 333 | 161±12.7 | 154±5.4 | 233±15.6 | 225±17.5 | 154±3.5 |
| | 1000 | 154±5.8 | 188±4.2 | 335±11.9 | 364±21.4 | 157±5.8 |
| | 1666 | | | | 414±32.8 | |
| | 3333 | 0±0.0 [b] | | 533±14.9 | 502±32.4 | 171±5.5 |
| | 6666 | toxic | | 477±39.8 | | 173±8.1 |
| Trial Summary | | Negative | Negative | Positive | Positive | Negative |
| Positive Control | | 503±5.2 | 1132±62.5 | 812±50.9 | 845±18.8 | 529±7.9 |
| TA98 | 0 | 28±2.2 | 32±6.1 | 35±2.7 | | 43±3.5 |
| | 10 | | 32±4.7 | | | |
| | 33 | | 41±5.5 | | | |
| | 100 | 30±3.5 | 32±0.3 | 36±3.5 | | 46±4.5 |
| | 333 | 35±2.9 | 29±0.6 | 34±2.9 | | 44±6.1 |
| | 1000 | 27±3.3 | 44±4.7 | 30±1.8 | | 50±5.8 |
| | 3333 | 23±3.4 [b] | | 39±3.8 | | 31±3.8 |
| | 6666 | toxic | | 29±3.5 | | 40±1.5 |
| Trial Summary | | Negative | Negative | Negative | | Negative |
| Positive Control | | 677±20.6 | 464±26.2 | 770±11.3 | | 168±3.5 |

[a] Revertants are presented as mean ± standard error from 3 plates

[b] Slight toxicity

**Remarks:** None

**CONCLUSIONS**

**Remarks:** The test substance gave a positive result only in the second experiment, which used a different concentration of S9 than the first experiment. Metabolic activation, specifically in the form of 30% Aroclor 1254-induced male Syrian hamster liver S9, was required to obtain the mutagenic response. 10% hamster S9 was ineffective, as was 10% or 30% S9 derived from the livers of pre-treated rats.

**DATA QUALITY**

- **Reliabilities:** 4, Not Assignable

**Remarks:** Secondary summary of published studies.

**REFERENCES**

Mortelmans, K., et al, Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environ. Mutagen. 8 (suppl. 7), 1-119 (1986)

Zeiger, E., et al, Salmonella mutagenicity tests: V. Results from the testing of chemicals. Environ. Mol. Mutagen. 19 (suppl. 2) 2-141, 1992

Reported in:

NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,2-bis(bromomethyl)-1,3-propanediol (FR-1138, CAS No. 3296-90-0) in F344/N Rats and B6C3F1 Mice (Feed Studies), NTP TR 452, National Toxicology Program, May 1996

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 4

## HUMAN HEALTH ENDPOINTS
## 15.5 GENETIC TOXICITY IN VITRO

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Radian Corporation

**METHOD**

- **Method:** Galloway et al (1987)
- **Test Type:** Cytogenetic Assay (Chromosomal Aberration)
- **System of testing:** Non-bacterial
- **GLP:** No data
- **Year:** 1987
- **Species/Strain:** Chinese Hamster Ovary cells
- **Metabolic activation:** S9-mix, Rat liver cells, Aroclor induced, and cofactor
- **Concentrations tested:** 400, 500, 600, 700 µg/ml (-S9), 600, 800, 1000, 1200 µg/ml (+S9)
- **Statistical Methods:** Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose.

**Remarks:**

- **Test Design**

  - **Number of replicates:** Single flask per dose, positive or equivocal results were repeated
  - **Positive Controls:** Mitomycin-C (-S9), Cyclophosphamide (+S9)
  - **Negative Control:** Solvent vehicle
  - **Solvent:** Dimethylsulfoxide
  - **Exposure Periods:** Expt 1: 18.5 hrs (-S9), 2hours (+S9); Expt 2 –S9, extra 10-12 hrs due to cell cycle delay

**RESULTS**

- **Result:** Positive
- **Cytotoxic concentration**

  - **With metabolic activation:** ≥ 700 µg/ml
  - **Without metabolic activation:** ≥ 1200 µg/ml

- **Genotoxic effects**

  - **With metabolic activation:** Significant ($P \leq 0.05$) dose-related increase in chromosomal aberrations.
  - **Without metabolic activation:** None

- **Statistical results:**

| -S9 | | | | | +S9 | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Dose (µg/ml) | Total Cells | No. of Abs [a] | Abs/ Cell | Cells with Abs (%) | Dose (µg/ml) | Total Cells | No. of Abs | Abs/ Cell | Cells with Abs (%) |
| Harvest time: 20.5 hours [b] | | | | | Harvest time: 10.5 hours | | | | |
| Summary: Negative | | | | | Summary: Positive | | | | |
| Dimethylsulfoxide | 100 | 2 | 0.02 | 2.0 | Dimethylsulfoxide | 100 | 5 | 0.05 | 5.0 |
| Mitomycin-C (0.062 µg/ml) | 50 | 10 | 0.20 | 16.0 | Cyclophosphamide (50 µg/ml) | 50 | 19 | 0.38 | 28.0 |
| 400 | 100 | 1 | 0.01 | 1.0 | 600 | 100 | 8 | 0.08 | 4.0 |
| 500 | 100 | 2 | 0.02 | 2.0 | 800 | 100 | 24 | 0.24 | 22.0* |
| 600 | 100 | 0 | 0.00 | 0.0 | 1000 | 100 | 17 | 0.17 | 16.0* |
| 700 | 0 | | | | 1200 | 0 | | | |
| | | | | P=0.833 [c] | | | | | P≤0.001 |

* Positive (P<0.05)

[a] Abs = aberrations

[b] Because of significant chemical-induced cell cycle delay, incubation time prior to addition of colcemid was lengthened to provide suffidient metaphase cells at harvest

[c] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

**Remarks:** A majority of the breaks that were observed in the study were located in the heterochromatic region of the long arm of the X chromosome. The authors did not know the reason for this preferential breakage site.

**CONCLUSIONS**

**Remarks:** The test substance induced chromosomal aberrations in CHO cells, in the presence of S9.

**DATA QUALITY**

- **Reliabilities:** 2, Valid with restrictions

**Remarks:** Study reported in literature (peer reviewed).

**REFERENCES**

Galloway, S.M., et al, Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environ. Mol. Mutagen., 10 (suppl. 10), 1 -175, 1987

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 5

**Remarks:**

## HUMAN HEALTH ENDPOINTS
## 15.6 GENETIC TOXICITY IN VITRO

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Radian Corporation

**METHOD**

- **Method:** Galloway et al (1987)
- **Test Type:** Cytogenetic Assay (Sister Chromatid exchange Test)
- **System of testing:** Non-bacterial
- **GLP:** No data
- **Year:** 1987
- **Species/Strain:** Chinese Hamster Ovary cells
- **Metabolic activation:** S9-mix, Rat liver cells, Aroclor induced, and cofactor
- **Concentrations tested:** 16.7, 50, 167, 500 µg/ml (-S9), 800, 1000, 1200 µg/ml (+S9)
- **Statistical Methods:** Significance of relative SCE/chromosome tested by the linear regression trend test vs. log of the dose.

**Remarks:**

- **Test Design**

  - **Number of replicates:** Single flask per dose, positive or equivocal results were repeated
  - **Positive Controls:** Mitomycin-C (-S9), Cyclophosphamide (+S9)
  - **Negative Control:** Solvent vehicle
  - **Solvent:** Dimethylsulfoxide
  - **Exposure Periods:** Expt 1: 26.3 hrs (-S9), 2hours (+S9); Expt 2 –S9, incubation time increased at 167 and 500 µg/kg due to significant chemical-induced cell cycle delay.

**RESULTS**

- **Result:** Equivocal
- **Cytotoxic concentration**

  - **With metabolic activation:** 1200 µg/ml
  - **Without metabolic activation:** ≥ 500 µg/ml

- **Genotoxic effects**

  - **With metabolic activation:** None
  - **Without metabolic activation:** Very slight increases in SCEs occurred at toxic levels

- **Statistical results:**

| Dose (µg/ml) | Total Cells | No. of Chromosomes | No. of SCEs [a] | SCEs/ Chromosome | SCEs/ Cell | Hrs in BrdU [a] | Relative change of SCEs/Chromosome [b] (%) |
|---|---|---|---|---|---|---|---|
| -S9 | | | | | | | |
| Summary: Negative | | | | | | | |
| Solvent | 50 | 1038 | 496 | 0.47 | 9.9 | 26.3 | |
| Positive control (0.005 µg/ml) | 25 | 519 | 692 | 1.33 | 27.7 | 26.3 | 179.03 |
| 16.7 | 50 | 1041 | 485 | 0.46 | 9.7 | 26.3 | -2.50 |
| 50 | 50 | 1042 | 498 | 0.47 | 10.0 | 26.3 | 0.02 |
| 167 | 50 | 1050 | 545 | 0.51 | 10.9 | 33.5 [c] | 8.62 |
| 500 | 0 | | | | | 33.5 [c] | |
| | | | | P=0.077 [d] | | | |
| +S9 | | | | | | | |
| Summary: Equivocal | | | | | | | |
| Solvent | 50 | 1050 | 496 | 0.47 | 9.9 | 25.5 | |
| Positive control (1.5 µg/ml) | 25 | 523 | 840 | 1.6 | 33.6 | 25.5 | 240.00 |
| 800 | 50 | 1048 | 556 | 0.53 | 11.1 | 25.5 | 12.31 |
| 1000 | 50 | 1047 | 590 | 0.56 | 11.8 | 25.5 | 19.29 |
| 1200 [e] | 50 | 1046 | 574 | 0.54 | 11.5 | 25.5 | 16.17 |
| | | | | P=0.004 | | | |

[a] SCE = sister chromatid exchange, BrdU = bromodeoxyuridine

[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells

[c] Due to chemical induced cell cycle delay, incubation time was extended to provide sufficient cells for scoring

[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

[e] Marked toxicity noted at this dose

**Remarks:** None

**CONCLUSIONS**

**Remarks:** The test substance did not induce sister chromatid exchanges in CHO cells without S9, even at doses that induced toxicity and marked cell cycle delay. Very slight increases in SCEs occurred at toxic levels with S9. The top dose, 1.2 mg/ml, reduced confluence by about 75%.

**DATA QUALITY**

- **Reliabilities:** 2, Valid with restrictions

**Remarks:** Study reported in literature (peer reviewed).

**REFERENCES**

Galloway, S.M., et al, Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: Evaluations of 108 chemicals. Environ. Mol. Mutagen., 10 (suppl. 10), 1 -175, 1987

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 6

**Remarks:**

## HUMAN HEALTH ENDPOINTS
## 15.7 GENETIC TOXICITY IN VITRO

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dead Sea Bromine Co.

**METHOD**

- **Method:**
- **Test Type:** Reverse Mutation Assay (Ames Test)
- **System of testing:** Bacterial
- **GLP:** No
- **Year:** 1977
- **Species/Strain:** Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537
- **Metabolic activation:** S9-mix, Rat liver cells, Aroclor induced
- **Concentrations tested:** 1, 10, 100, 500 µg/plate
- **Statistical Methods:** No data

**Remarks:**

- **Test Design**
  - **Number of replicates:** 2
  - **Positive Controls:** N-methyl-N'-nitroso-N-nitrosoguanidine (-S9)
    Daunomycin (-S9)
    Acridine-orange (+S9)
  - **Negative Control:** Solvent vehicle
- **Solvent:** Dimethylsulfoxide

**RESULTS**

- **Result:** Negative
- **Cytotoxic concentration**
  - **With metabolic activation:** > 500 µg/plate
  - **Without metabolic activation:** > 500 µg/plate
- **Genotoxic effects**
  - **With metabolic activation:** None
  - **Without metabolic activation:** None
- **Statistical results:** All strains yielded colony counts that were not significantly different from the comparable control counts.

| Type of experiment | Microsome preparation | Compound* | µg/plate | No. of revertant colonies per plate** | | | |
|---|---|---|---|---|---|---|---|
| | | | | TA98 | TA100 | TA1535 | TA1537 |
| Solvent controls | - | DMSO | | 30; 58 | 203; 247 | 91; 103 | 14; 16 |
| | + | DMSO | | 32; 55 | 185; 164 | 19; 21 | 8; 12 |
| Positive controls | - | MNNG | 2 | | 10038; 12500 | 7500; 8500 | |
| | - | Daunomycin | 5 | 474; 510 | | | |
| | - | AO | 20 | 96; 107 | | | |
| | + | AO | 20 | 1447; 1710 | 1778; 1965 | 28; 42 | 95; 103 |
| Test runs | - | DBNPG | 500 | 34; 48 | 222; 248 | 89; 90 | 19; 19 |
| | + | '' | 500 | 35; 49 | 111; 154 | 14; 24 | 7; 9 |
| | - | '' | 100 | 42; 45 | 238; 284 | 62; 93 | 6; 19 |
| | + | '' | 100 | 45; 56 | 167; 183 | 20; 21 | 8; 9 |
| | - | '' | 10 | 37; 39 | 212; 241 | 52; 74 | 25; 26 |
| | + | '' | 10 | 52; 56 | 164; 168 | 17; 22 | 7; 13 |
| | - | '' | 1 | 41; 51 | 219; 233 | 56; 67 | 9; 11 |
| | + | '' | 1 | 49; 52 | 175; 185 | 19; 23 | 7; 11 |

MMNG = N-methyl-N'-nitroso-N-nitrosoguanidine, AO = Acridine-orange

**Remarks:** None

**CONCLUSIONS**

**Remarks:** None

**DATA QUALITY**

- **Reliabilities:** 3, Not reliable

**Remarks:** No details on purity of test substance or lot number used. Test not subject to QA overview. Substance only tested to 500 µg/plate.

**REFERENCES**

Israel Institute for Biological Research, Ames salmonella/microsome mutagenicity assay for Dibromo neo-pentyl glycol (DBNPG), October 1977

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 7

**Remarks:**

## HUMAN HEALTH ENDPOINTS
## 15.8 GENETIC TOXICITY IN VITRO

**TEST SUBSTANCE**

- Monobromopentaerythritol

**Remarks:** Purity: 98.2%, Lot No.: 564-347-01
Source: Bromine Compounds Ltd.
This study is provided as additional information from a structurally similar compound.

**METHOD**

- **Method:** OECD 471, 92/69/EEC Method B14, US EPA, Method: HG-Gene Muta – S. typhimurium: The Salmonella typhimurium reverse mutation assay, 1984
- **Test Type:** Reverse Mutation Assay
- **System of testing:** Bacterial
- **GLP:** Yes
- **Year:** 1996
- **Species/Strain:** Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537
- **Metabolic activation:** S9-mix, Rat liver cells, Aroclor induced
  S9-mix, Hamster liver cells, uninduced
- **Concentrations tested:** 50, 150, 500, 1500, 5000 µg/plate
- **Statistical Methods:** None

**Remarks:**

- **Test Design**

  - **Number of replicates:** 3
  - **Positive Controls:** N-ethyl-N'-nitroso-N-nitrosoguanidine (TA100, TA1535, -S9)
    9-aminoacridine (TA1537, -S9)
    2-nitrofluorene (TA98, -S9)
    2-aminoanthracene (TA98, TA100, TA 1535, TA1537, +S9)
    Congo red (TA98, +S9)
  - **Negative Control:** Solvent vehicle

- **Solvent:** Dimethylsulfoxide

**RESULTS**

- **Result:** Negative
- **Cytotoxic concentration**

  - **With metabolic activation:** > 5000 µg/plate
  - **Without metabolic activation:** > 5000 µg/plate

- **Genotoxic effects**
  - **With metabolic activation:** None
  - **Without metabolic activation:** None

- **Statistical results:**

| Strain | Dose level (µg/plate) | Revertants/Plate [a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Test 1 | | | | Test 2 | | | |
| | | -S9 | +10% Rat S9 | +10% Hamster S9 | +30% Hamster S9 | -S9 | +10% Rat S9 | +10% Hamster S9 | +30% Hamster S9 |
| TA1535 | 5000 | 12±1.2 | 14±4.2 | 9±3.2 | 15±0.0 | 14±4.2 | 18±3.6 | 16±6.7 | 13±2.6 |
| | 1500 | 14±2.1 | 13±1.2 | 12±1.5 | 11±3.2 | 13±4.5 | 15±4.2 | 15±3.0 | 15±2.9 |
| | 500 | 9±3.8 | 12±2.3 | 11±3.1 | 10±4.7 | 9±6.8 | 12±2.9 | 16±2.5 | 16±3.8 |
| | 150 | 9±2.3 | 12±3.1 | 12±5.3 | 10±5.5 | 10±0.6 | 13±1.7 | 13±2.0 | 15±2.1 |
| | 50 | 8±1.2 | 12±2.6 | 13±1.7 | 11±2.6 | 11±1.0 | 13±3.5 | 17±4.5 | 11±1.5 |
| | 0 | 11±3.1 | 16±0.0 | 15±6.1 | 16±1.5 | 14±5.5 | 16±0.6 | 17±0.6 | 15±2.5 |
| | Solvent | 12±2.0 | 12±1.5 | 12±0.6 | 16±2.1 | 13±2.3 | 17±1.5 | 12±2.5 | 18±2.1 |
| | ENNG (5.0) | 516±71.7 | | | | 1151±130.3 | | | |
| | AA (2.0) | | 92±8.0 | 102±60.1 | 131±9.3 | | 120±19.7 | 86±17.6 | 146±36.0 |
| TA1537 | 5000 | 12±6.8 | 13±1.5 | 10±3.0 | 8±3.1 | 9±1.0 | 15±2.6 | 11±1.7 | 8±5.6 |
| | 1500 | 13±3.0 | 12±2.3 | 9±2.5 | 12±4.5 | 10±1.5 | 14±6.7 | 11±1.2 | 12±1.5 |
| | 500 | 9±1.2 | 7±1.0 | 11±4.2 | 11±2.6 | 8±1.5 | 11±0.6 | 10±2.6 | 11±3.8 |
| | 150 | 12±0.6 | 11±1.2 | 10±2.3 | 11±1.7 | 11±6.5 | 12±7.0 | 14±4.4 | 12±5.0 |
| | 50 | 10±1.5 | 9±3.2 | 12±1.5 | 9±2.1 | 7±2.1 | 11±5.6 | 12±2.6 | 11±2.5 |
| | 0 | 9±1.0 | 14±4.0 | 9±1.0 | 11±4.4 | 14±3.6 | 15±5.5 | 12±3.2 | 15±4.0 |
| | Solvent | 11±2.5 | 11±1.7 | 13±3.6 | 12±3.2 | 13±3.5 | 15±4.0 | 17±0.6 | 17±3.1 |
| | 9 AC (80.8) | X | | | | X | | | |
| | AA (2.0) | | 45±4.4 | 151±41.6 | 99±43.9 | | 72±18.7 | 135±14.4 | 98±23.4 |
| TA98 | 5000 | 32±4.0 | 27±4.6 | 28±2.0 | 25±3.1 | 24±4.9 | 28±4.6 | 22±2.1 | 27±7.2 |
| | 1500 | 22±6.5 | 23±3.8 | 26±1.7 | 27±9.0 | 25±4.0 | 25±2.3 | 22±3.2 | 24±2.6 |
| | 500 | 26±7.5 | 21±4.2 | 22±3.5 | 25±4.0 | 22±5.5 | 24±6.4 | 21±3.2 | 28±1.7 |
| | 150 | 18±0.6 | 26±6.6 | 26±0.6 | 26±4.6 | 23±2.5 | 26±5.2 | 23±3.2 | 24±4.5 |
| | 50 | 23±4.5 | 25±4.7 | 20±5.5 | 22±3.2 | 19±2.1 | 26±3.0 | 21±1.7 | 25±5.3 |
| | 0 | 22±2.6 | 22±2.1 | 28±4.5 | 23±4.7 | 23±4.0 | 23±2.9 | 24±4.0 | 25±2.5 |
| | Solvent | 25±3.8 | 24±3.2 | 27±4.0 | 27±4.4 | 24±2.1 | 27±4.2 | 25±2.0 | 27±3.8 |
| | NF (1.0) | 152±2.1 | | | | 388±15.6 | | | |
| | AA (0.5) | | 159±25.3 | 367±32.7 | 114±0.0 | | 175±8.1 | 675±15.3 | 430±71.2 |
| | CR (200.0) | | 24±3.0 | 43±3.2 | 124±7.0 | | 48±6.7 | 57±2.1 | 126±44.7 |
| TA100 | 5000 | 107±2.6 | 113±6.8 | 128±5.1 | 117±7.8 | 118±11.8 | 111±0.6 | 117±10.1 | 146±9.8 |
| | 1500 | 104±4.0 | 114±27.7 | 117±25.0 | 118±6.1 | 110±9.2 | 110±16.3 | 124±6.2 | 127±2.1 |
| | 500 | 112±14.6 | 116±4.4 | 114±7.6 | 117±10.7 | 106±6.0 | 113±11.9 | 109±6.9 | 122±27.3 |
| | 150 | 114±6.8 | 108±5.5 | 117±6.6 | 119±2.3 | 114±7.5 | 124±12.1 | 119±2.0 | 134±6.8 |
| | 50 | 110±6.7 | 113±10.2 | 105±3.2 | 105±8.1 | 113±6.1 | 111±1.5 | 110±9.6 | 127±10.5 |
| | 0 | 109±5.0 | 103±12.2 | 129±20.8 | 119±8.5 | 127±6.1 | 128±7.5 | 133±12.6 | 136±9.3 |
| | Solvent | 110±11.7 | 129±4.2 | 109±11.2 | 130±7.5 | 112±6.7 | 120±4.0 | 129±10.3 | 142±8.9 |
| | ENNG (3.0) | 328±4.0 | | | | 596±31.3 | | | |
| | AA (1.0) | | 332±28.1 | 560±135.2 | 293±107.7 | | 433±56.1 | 915±124.4 | 801±130.8 |

[a] Data presented as mean ± standard deviation

ENNG N-ethyl-N'-nitro-N-nitrosoguanidine, 9 AC 9-aminoacridine, NF 2-nitrofluorene, AA 2-aminoanthracene, CR Congo red

X Too many colonies to count accurately

**Remarks:** No substantial increases in revertant colony numbers of any of the tester strains were observed following treatment with monobromopentaerythritol at any dose level, in the presence or absence of S-9 mix, in either mutation test. The concurrent positive control compounds demonstrated the sensitivity of the assay and the metabolizing activity of the liver preparations.

**CONCLUSIONS**

**Remarks:** It is concluded that, when tested in dimethylsulfoxide, the test substance shows no evidence of mutagenic activity in this bacterial system.

**DATA QUALITY**

- **Reliabilities:** 1, Reliable without restrictions

**Remarks:** Study conducted under GLP to OECD/EC/EPA test guidelines by Huntingdon Life Sciences.

## HUMAN HEALTH ENDPOINTS
## 16.1 REPEATED DOSE TOXICITY

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dow Chemical Company, Lot No.: 840429-162, Purity: approximately 78.6%, Identity of impurities: 2,2-bis (hydroxymethyl)-1-bromo-3-hydroxypropane (6.6%), 2,2-bis (bromomethyl)-1-bromo-3-hydroxypropane (6.9%), pentaerythritol (0.2%), dimers and structural isomers (7.7%).

**METHOD**

- **Method/guideline followed:** Similar to OECD 453, however neither neurological nor ocular assessments were made during the study.
- **Test type:** 2 year repeated dose toxicity and carcinogenicity study
- **GLP:** Yes
- **Year:** 1991
- **Species:** Rat, Mouse
- **Strain:** F344/N (rat), B6C3F$_1$ (Mouse)
- **Route of administration:** Oral feed
- **Duration of test:** 2 years
- **Doses/concentration levels:**

Rat – 0, 2500, 5000, 10000 ppm
Rat (stop exposure evaluation) – 20000 ppm
Mouse – 0, 312, 625, 1250 ppm

- **Sex:** Male/female (rat/mouse), male rats used in stop-exposure evaluation
- **Exposure period:** 104/105 weeks, 3 months for stop-exposure evaluation
- **Frequency of treatment:** Continuous, ad libitum
- **Control group and treatment:**

Rats - 70 male/60 female, feed control
Mice – 60 male/60 female, feed control

- **Post exposure observation period:** None
- **Statistical methods:** Kaplan & Meier product-limit procedure (probability of survival, estimate of neoplasm incidence). Cox's method for testing 2 groups for equality and Tarone's life table test (dose-

related trends). Dinse & Lagakos, Dinse & Haseman prevalence analysis ( time-specific neoplasm incidences). Fisher exact test, Cochran-Armitage trend test. Dunnett and Williams parametric multiple comparisons (organ & body weights). Shirley and Dun's non-parametric multiple comparison methods (clinical chemistry, urinalysis, spermatid and epididymal spermatozoa data). Jonckheere's test (significance of dose-related trends). Mann-Whitney U test (average severity values). Morrison multivariate analysis of variance (treatment effects).

**Remarks:**

- **Test subjects**

  - **Age at study initiation:** Rats/mice – 6 weeks old

  - **No. of animals/sex/dose:** Rats/mice - 60 male/60 female per dose. 70 male rats were used in the stop exposure evaluation.

- **Study Design**

  - **Vehicle:** Feed

  - **Satellite groups and reasons they were added:** A group of 70 male rats received 20000 ppm in feed for 3 months. 10 rats (and 10 male controls) were evaluated at this time and the remaining rats were fed control feed for the remainder of the study. Group added to evaluate the potential for progression or regression of urinary bladder and kidney lesions.

  - **Clinical observations performed and frequency:** Observed twice daily; body weights and clinical observations recorded initially, weekly for weeks 2 to 13, monthly thereafter, and at the end of the studies. Feed consumption was measured every 4 weeks by cage.

  - **Organs examined at necropsy (macroscopic and microscopic):** Complete histopathologic examinations were performed on all animals necropsied. In addition to gross lesions, tissue masses and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon and rectum), liver, lung, lymph nodes (mandibular or mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial or clitoral gland, prostate gland, salivary gland, skin, small intestine, (duodenum, jejunum and ileum), spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder and uterus.

**RESULTS**

- **NOAEL (rats):** Not achieved
- **LOAEL (rats):** 2500 ppm
- **NOAEL (mice):** Not achieved
- **LOAEL (mice):** 312 ppm

- **Actual dose received by sex:**
  Rats – 100, 200, 430 mg/kg bw (male); 115, 230, 460 mg/kg (female); 800 mg/kg bw (Stop exposure males)
  Mice – 35, 70, 140 mg/kg bw (male); 40, 80, 170 mg/kg bw (female)

- Toxic response/effects by dose level:

- Statistical results, as appropriate:

**Remarks:**

- **Body weight:**
  Rats – Mean body weights of exposed male and female rats receiving 10000 ppm and stop exposure males receiving 20000 were lower than th ose of the controls throughout most of the study.
  Mice – Mean body weights of exposed male and female mice were similar to controls throughout the study. Final mean bodyweights were also generally similar to those of controls.

- **Food/water consumption:**
  Rats – In the continuous exposure study, feed consumption by exposed rats was generally similar to that by the controls throughout the study. In 20000-ppm stop exposure males, the feed consumption was lower than that by controls.
  Mice – Feed consumption by exposed male and female mice was similar to that by controls.

- **Description, severity, time of onset and duration of clinical signs:**
  Rats – Clinical findings included skin and subcutaneous tissue masses on the face, tail and the ventral and dorsal surfaces of exposed rats.
  Mice – Clinical findings included swelling, discharge and tissue masses involving the eye in exposed mice.

- **Ophthalmologic findings, incidence and severity:** No data

- **Hematologic findings, incidence and severity:** No data

- **Clinical biochemistry findings, incidence and severity:** No data

- **Mortality and time to death:**
  Rats – Survival of 5000 and 1000 continuous exposure males and females and 20000-ppm stop exposure males was significantly lower than controls.
  Mice – Survival of 1250-ppm males and females was significantly lower than controls.

Rat survival

| | Males | | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Dose (ppm) | | | | | Dose (ppm) | | | |
| | 0 | 2500 | 5000 | 10000 | 20000[a] | 0 | 2500 | 5000 | 10000 |
| Animals initially in study | 70 | 60 | 60 | 60 | 70 | 60 | 60 | 60 | 60 |
| 3 month interim evaluation[b] | 10 | 0 | 0 | 0 | 10 | | | | |
| 15 month interim evaluation[b] | 9 | 7 | 9 | 5 | 0 | 10 | 9 | 7 | 8 |
| Moribund | 24 | 30 | 36 | 43 | 55 | 14 | 22 | 27 | 41 |
| Natural deaths | 1 | 3 | 2 | 11 | 5 | 0 | 2 | 3 | 6 |
| Animals surviving to study termination | 26 | 20 | 13 | 1 | 0 | 36 | 27 | 23 | 5 |
| Percentage probability of survival at the end of the study[c] | 51 | 38 | 26 | 2 | 0 | 72 | 53 | 43 | 10 |
| Mean survival (days)[d] | 688 | 652 | 669 | 587 | 544 | 711 | 701 | 676 | 630 |
| Survival analysis[e] | P<0.001 | P=0.126 | P=0.010 | P<0.001 | P<0.001 | P<0.001 | P=0.095 | P=0.005 | P<0.001 |

[a] Ten male rats receiving 20000 ppm test substance in feed were evaluated at 3 months. The remaining 60 male rats received control feed until the end of the 2 year study. [b] censored from survival analysis. [c] Kaplan-Meier determinations. [d] Mean of all deaths (uncensored, censored and terminal sacrifice). [e] The result of the life table trend test (Tarone, 1975) is in the control column and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns.

Mouse survival

| | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Dose (ppm) | | | | Dose (ppm) | | | |
| | 0 | 312 | 625 | 1250 | 0 | 312 | 625 | 1250 |
| Animals initially in study | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| 15 month interim evaluation [a] | 10 | 9 | 10 | 10 | 8 | 10 | 9 | 10 |
| Accidental deaths [a] | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Missing [a] | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Moribund | 3 | 12 | 11 | 13 | 9 | 14 | 14 | 29 |
| Natural deaths | 5 | 3 | 4 | 5 | 6 | 6 | 11 | 10 |
| Animals surviving to study termination | 42 | 36 | 35 | 30 | 37 | 30 | 26 | 11 |
| Percentage probability of survival at the end of the study [b] | 84 | 71 | 70 | 63 | 71 | 60 | 51 | 22 |
| Mean survival (days) [c] | 710 | 675 | 698 | 684 | 690 | 685 | 691 | 625 |
| Survival analysis [d] | P=0.054 | P=0.169 | P=0.174 | P=0.038 | P<0.001 | P=0.422 | P=0.117 | P<0.001 |

[a] Censored from survival analyses. [b] Kaplan-Meier determinations. [c] Mean of all deaths (uncensored, censored and terminal sacrifice). [d] The result of the life table trend test (Tarone, 1975) is in the control column and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns.

- **Gross pathology incidence and severity:** No data, although it is likely that some or all the neoplasms found would be visible macroscopically.

- **Organ weight changes:**
  Rats – At the 3-month interim evaluation, the right kidney and liver weights of 20000-ppm stop-exposure males were significantly lower ($P \leq 0.01$) than controls. The right kidney and liver weights relative to bodyweight in this group were significantly higher ($P \leq 0.01$) than controls. At the 15-month interim evaluation, the relative right kidney weights in 10000-ppm males and females were significantly higher than controls. The relative liver weights in 5000 and 10000-ppm males and 2500, 5000 and 10000 females were significantly higher ($P \leq 0.05$ & $P \leq 0.01$, respectively) than controls.
  Mice – No significant differences.

- **Histopathology incidence and severity:**

  Rats:
  Skin: The incidence of squamous cell papilloma in 20000-ppm stop-exposure males was significantly greater than controls. The incidences of keratocanthoma and of squamous and basal cell neoplasms (combined) in 5000 and 10000-ppm continuous-exposure males and in the 20000-ppm stop-exposure males were significantly greater than controls.

  Mammary Gland: The incidences of benign mammary gland neoplasms (fibroadenoma and fibroadenoma or adenoma (combined)) were significantly greater in the stop-exposure group of male rats and in all continuous-exposure groups of male rats than controls. In female rats, the incidences of fibroadenoma and of fibroadenoma, adenoma, or carcinoma (combined) in all exposed groups

were greater than controls. The incidences of multiple fibroadenoma in all exposed female groups were greater than controls.

Zymbal's Gland: The incidences of Zymbal's gland adenoma in 10000-ppm males and of adenoma or carcinoma in 20000-ppm stop-exposure males were significantly greater than those in the controls.

Oral cavity (Pharynx, Tongue and Gingiva), Esophagus and Forestomach: The incidences of squamous cell papilloma of the oral cavity in exposed males (continuous and stop-exposure) were significantly greater than controls. Additionally, the incidences of squamous cell papilloma of the esophagus in male and female rats exposed to 10000 ppm were significantly greater than controls. The incidences of squamous cell neoplasms of the oral cavity in 20000-ppm stop-exposure males were similar to those in 10000-ppm males. Squamous cell papilloma of the forestomach occurred in exposed groups of rats, but the incidence was only significant in 20000-ppm stop-exposure males.

Small and Large Intestine: There was a significant positive trend in the incidences of adenoma (adenomateous polyp) in the large intestine of males. In 20000-ppm stop-exposure males, the incidence of adenoma and adenoma or carcinoma (combined) of the large intestine was significantly greater than controls.

Kidney and Urinary Bladder: In male rats, the incidence of renal tubule adenoma in the 10000-ppm group was marginally but significantly greater than controls.

Lung: The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 10000-ppm continuous exposure males and 20000-ppm stop-exposure males were significantly greater than controls.

Thyroid Gland: In males, the incidence of follicular cell adenoma in the 20000-ppm stop-exposure group and the incidence of follicular cell adenoma or carcinoma in 5000-ppm continuous-exposure males, 20000-ppm stop-exposure males and 10000-ppm females were significantly greater than controls.

Hematopoietic System: The incidences of mononuclear cell leukemia in male rats from the 5000 and 10000-ppm continuous-exposure groups and the 20000 stop-exposure group were significantly greater than controls.

Pancreas: The incidences of hyperplasia in all exposed groups of male rats were significantly greater than controls.

Summary of study findings - Rats

| | Males Dose (ppm) | | | | | Females Dose (ppm) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0 | 2500 | 5000 | 10000 | 20000 | 0 | 2500 | 5000 | 10000 |
| **Nonneoplastic effects** | | | | | | | | | |
| Kidney | | | | | | | | | |
| Focal atrophy | 0/51 | 0/53 | 0/51 | 5/55 | 0/59 | 0/50 | 2/51 | 1/53 | 7/52 |
| Papillary degeneration | 0/51 | 5/53 | 30/51 | 29/55 | 16/59 | 0/50 | 1/51 | 3/53 | 17/52 |
| Papillary epithelial hyperplasia | 10/51 | 20/53 | 25/51 | 47/55 | 21/59 | 0/50 | 1/51 | 1/53 | 7/52 |
| Pelvis, transitional epithelium, hyperplasia | 0/51 | 0/53 | 0/51 | 4/55 | 4/59 | | | | |
| Lung | | | | | | | | | |
| Alveolar/bronchiolar hyperplasia | 3/51 | 4/53 | 5/51 | 7/55 | 14/60 | | | | |
| Thyroid Gland | | | | | | | | | |
| Follicular cell hyperplasia | 1/51 | 0/53 | 2/51 | 5/55 | 6/59 | | | | |
| Seminal Vesicle | | | | | | | | | |
| Hyperplasia | 1/51 | 6/53 | 4/51 | 16/55 | 33/60 | | | | |
| Pancreas | | | | | | | | | |
| Focal hyperplasia | 3/51 | 9/53 | 12/51 | 14/53 | 27/59 | | | | |
| Forestomach | | | | | | | | | |
| Mucosal hyperplasia | 4/51 | 12/53 | 6/51 | 6/55 | 6/59 | | | | |
| Urinary Bladder | | | | | | | | | |
| Hyperplasia | 0/51 | 0/53 | 1/51 | 3/55 | 10/59 | | | | |
| **Neoplastic effects** | | | | | | | | | |
| Skin | | | | | | | | | |
| Squamous cell papilloma, keratocanthoma, trichoepithelioma, basal cell adenoma, basal or squamous cell carcinoma | 4/51 | 6/53 | 14/51 | 24/55 | 21/60 | | | | |
| Skin, Subcutaneous Tissue | | | | | | | | | |
| Fibroma, fibrosarcoma or sarcoma | 2/51 | 9/53 | 13/51 | 16/55 | 10/60 | | | | |
| Mammary Gland | | | | | | | | | |
| Fibroadenoma or adenoma | 0/51 | 4/53 | 7/51 | 7/55 | 5/60 | | | | |
| Fibroadenoma | | | | | | 25/50 | 45/51 | 46/53 | 45/52 |
| Zymbal's Gland | | | | | | | | | |
| Adenoma or carcinoma | 2/51 | 1/53 | 4/51 | 5/55 | 15/60 | | | | |
| Oral Cavity (pharynx, tongue or gingiva) | | | | | | | | | |
| Squamous cell papilloma or carcinoma | 0/51 | 4/53 | 9/51 | 10/55 | 13/60 | 2/50 | 3/51 | 5/53 | 6/52 |
| Esophagus | | | | | | | | | |
| Squamous cell papilloma | 0/51 | 0/53 | 1/51 | 5/55 | 0/60 | 0/50 | 0/51 | 1/53 | 10/52 |
| Forestomach | | | | | | | | | |
| Squamous cell papilloma | 0/51 | 0/53 | 0/51 | 1/55 | 5/60 | | | | |
| Large Intestine | | | | | | | | | |
| Adenoma or carcinoma | 0/51 | 0/53 | 3/51 | 4/55 | 11/59 | | | | |
| Small Intestine | | | | | | | | | |
| Adenoma or carcinoma | 0/51 | 0/53 | 0/51 | 2/53 | 5/59 | | | | |
| Malignant Mesothelioma | 0/51 | 3/53 | 8/51 | 9/55 | 25/60 | | | | |
| Urinary Bladder | | | | | | | | | |
| Transitional cell papilloma or carcinoma | 0/51 | 0/53 | 1/51 | 3/55 | 2/59 | | | | |
| Lung | | | | | | | | | |
| Alveolar/bronchiolar adenoma or carcinoma | 1/51 | 1/53 | 3/51 | 4/55 | 7/60 | | | | |
| Squamous cell carcinoma | 0/51 | 0/53 | 0/51 | 0/55 | 3/60 | | | | |
| Thyroid Gland | | | | | | | | | |
| Follicular cell adenoma or carcinoma | 0/51 | 2/53 | 6/51 | 3/55 | 9/59 | 0/50 | 0/51 | 2/53 | 4/52 |
| Seminal Vesicle | | | | | | | | | |
| Adenoma or carcinoma | 0/51 | 0/53 | 0/51 | 0/55 | 2/60 | | | | |
| Hematopoietic System | | | | | | | | | |
| Mononuclear cell leukemia | 27/51 | 29/53 | 40/51 | 34/55 | 25/60 | | | | |
| **Uncertain effects** | | | | | | | | | |
| Kidney (renal tubule) | | | | | | | | | |
| Adenoma | 0/51 | 0/53 | 1/51 | 3/55 | 1/59 | | | | |
| Pancreas | | | | | | | | | |
| Acinar cell adenoma | 1/51 | 2/53 | 4/51 | 3/53 | 3/59 | | | | |

Mice:
Harderian Gland: The incidences of harderian gland adenoma in male and female mice exposed to 625 and 1250 ppm were significantly greater than controls. The incidence of harderian gland carcinoma in 1250-ppm females was significantly greater that controls. In 625-ppm and 1250-ppm males and in all female exposure groups, the incidences of adenoma or carcinoma 9combined) were significantly greater than those in the control groups.

Lung: The incidences of alveolar/bronchiolar adenoma and of alveolar/bronchiolar adenoma of carcinoma (combined) in 1250-ppm males and females and 625 ppm females were significantly greater than controls. In males exposed to 1250 ppm the incidences of multiple adenoma and of alveolar/bronchiolar carcinoma were significantly greater than controls. At 2 years, the incidences of alveolar epithelial hyperplasia in 625 and 1250-ppm females were significantly greater than controls.

Skin: The incidence of subcutaneous tissue sarcoma and the combined incidences of fibrosarcoma or sarcoma in 1250-ppm female mice were significantly greater than controls.

Forestomach: The incidences of squamous cell papilloma of the forestomach in 625 and 1250-ppm female mice were significantly greater that controls. In 1250-ppm males, the incidence of squamous cell papilloma or squamous cell carcinoma (combined) was significantly greater than controls.

Other: The incidence of hemangioma or hemangiosarcoma (combined) was significantly increased in 1250-ppm female mice.

Summary of study findings - Mice

| | Males Dose (ppm) | | | | Females Dose (ppm) | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 312 | 625 | 1250 | 0 | 312 | 625 | 1250 |
| **Nonneoplastic effects** | | | | | | | | |
| Lung | | | | | | | | |
| Alveolar epithelium, hyperplasia | | | | | 1/52 | 3/50 | 8/51 | 15/50 |
| **Neoplastic effects** | | | | | | | | |
| Harderian Gland | | | | | | | | |
| Adenoma or carcinoma | 4/50 | 7/51 | 16/50 | 22/49 | 3/52 | 12/50 | 13/51 | 19/50 |
| Skin, Subcutaneous Tissue | | | | | | | | |
| Sarcoma | | | | | 0/52 | 1/50 | 4/51 | 11/50 |
| Lung | | | | | | | | |
| Alveolar/bronchiolar adenoma or carcinoma | 15/50 | 11/51 | 16/50 | 25/49 | 5/52 | 5/50 | 15/51 | 19/50 |
| Kidney (renal tubule) | | | | | | | | |
| Adenoma | 0/50 | 0/51 | 3/50 | 2/49 | | | | |
| **Uncertain effects** | | | | | | | | |
| Forestomach | | | | | | | | |
| Squamous cell papilloma or carcinoma | 0/50 | 3/51 | 3/50 | 4/49 | | | | |
| Squamous cell papilloma | | | | | 0/52 | 1/50 | 5/51 | 3/50 |
| Mammary Gland | | | | | | | | |
| Carcinoma | | | | | 0/52 | 0/50 | 1/51 | 3/50 |
| Circulatory System | | | | | | | | |
| Hemangioma and hemangiosarcoma | | | | | 1/52 | 2/50 | 0/51 | 5/50 |

**CONCLUSIONS**

**Remarks:**

There was clear evidence of carcinogenic activity of the test substance in male F344/N rats based on increased incidences of neoplasms of the skin, subcutaneous tissue, mammary gland, Zymbal's gland, oral cavity, esophagus, forestomach, small and large intestines, mesothelium, urinary bladder, lung, thyroid gland and seminal vesicle, and the increased incidence of mononuclear cell leukemia.

There was clear evidence of carcinogenic activity of the substance in female F344/N rats based on increased incidences of neoplasms of the oral cavity, esophagus, mammary gland and thyroid gland.

There was clear evidence of carcinogenic activity of the substance in male B6C3$F_1$ mice based on increased incidences of neoplasms of the harderian gland, lung and kidney.

There was clear evidence of carcinogenic activity of the substance in female B6C3$F_1$ mice based on increased incidences of neoplasms of the harderian gland, lung and subcutaneous tissue.

Slight increases in the incidences of neoplasms in the pancreas and kidney in male mice and the forestomach, mammary gland and circulatory system in female mice may also have been related to treatment.

**DATA QUALITY**

- 1, Valid without restrictions

**Remarks:** Well-conducted study performed by Southern Research Institute.

**REFERENCES:**

NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,2-bis(bromomethyl)-1,3-propanediol (FR-1138, CAS No. 3296-90-0) in F344/N Rats and B6C3F1 Mice (Feed Studies), NTP TR 452, National Toxicology Program, May 1996

**OTHER:**

- **Last Changed:** October 4 2002
- **Order number for sorting:** 1

**Remarks:**

**REFERENCES**

Huntingdon Life Sciences Ltd., Monobromopentaerythritol, Bacterial Mutation Assay, January 1996

**OTHER**

- **Last Changed:** October 3 2002
- **Order number for sorting:** 8

**Remarks:** S-9 is usually only prepared from a rat previously treated with a compound (Aroclor) known to induce a high level of enzymic activity. However in this study S-9 mix using liver fraction from uninduced Syrian hamsters was also used as it was suspected that the test substance may be metabolised to a mutagen by hamster S-9 but not by rat.

## HUMAN HEALTH ENDPOINTS
## 16.2 REPEATED DOSE TOXICITY

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dow Chemical Company, Lot No.: 840429-162, Purity: approximately 78.6%, Identity of impurities: 2,2-bis (hydroxymethyl)-1-bromo-3-hydroxypropane (6.6%), 2,2-bis (bromomethyl)-1-bromo-3-hydroxypropane (6.9%), pentaerythritol (0.2%), dimers and structural isomers (7.7%).

**METHOD**

- **Method/guideline followed:** Similar to OECD 408, however ophthalmologic examination, sensory reactivity, grip strength and motor activity assessments were not performed.
- **Test type:** 13 Week repeated dose oral toxicity study
- **GLP:** Yes
- **Year:** 1986
- **Species:** Rat, Mouse
- **Strain:** F344/N (rat), B6C3$F_1$ (Mouse)
- **Route of administration:** Oral feed
- **Duration of test:** 13 weeks
- **Doses/concentration levels:**

Rat – 0, 1250, 2500, 5000, 10000, 20000 ppm
Mouse – 0, 625, 1250, 2500, 5000, 10000 ppm

- **Sex:** Male/female (rat/mouse)
- **Exposure period:** 13 weeks
- **Frequency of treatment:** Continuous, ad libitum
- **Control group and treatment:** 10 male/10 female, feed control (rat/mouse)
- **Post exposure observation period:** None
- **Statistical methods:** Williams' or Shirley's test, Dunnett's or Dunn's test (body weight, organ weights, clinical chemistry, urinalysis, sperm data), Fisher exact test (incidence of lesions), Mann Whitney U test (severity values), multivariate analysis of variables (vaginal cytology data)

**Remarks:**

- **Test subjects**

  - **Age at study initiation:** Rat – 6 weeks
    Mouse – 6 weeks

  - **No. of animals/sex/dose:** 10 male/10 female per dose (rat/mouse)

- **Study Design**

  - **Vehicle:** Feed

  - **Satellite groups and reasons they were added:** Special clinical chemistry and Urinalysis study group (rats only)

  - **Clinical observations performed and frequency:** Observed twice daily; animals were weighed initially, weekly and at the end of the studies. Clinical observations were recorded weekly. Feed consumption was measured weekly by cage. At the end of the 13-week studies, blood was collected from the retro-orbital sinus and urine was collected from all rats and mice. In the special study rats, blood was collected on days 3, 15, 30, 60 and at study termination. Urine samples were collected on days 3, 15, 30 and 60 and at study termination. Additional urine samples were collected for measurement of urinary concentrating ability following 16-hour water deprivation periods.
    **Clinical chemistry:** albumin, albumin/globulin ratio, creatinine (rats only), globulin, glucose, total protein, and urea nitrogen.
    **Urinalysis:** glucose, protein, specific gravity and volume.

    Sperm and vaginal fluid samples were evaluated in 0, 5000, 10000 and 20000-ppm rats and 0, 2500, 5000 and 10000-ppm mice at the end of the studies. The parameters evaluated in males were sperm count, morphology and motility. The right cauda, right epididymis and right testis were weighed. Vaginal fluid samples were collected for up to 7 consecutive days prior to the end of the studies for vaginal cytology evaluations. The parameters evaluated in females were relative frequency of estrous stages and estrous cycle length.

  - Organs examined at necropsy (macroscopic and microscopic): Organs weighed included brain, heart right kidney, liver lung, spleen, right testis and thymus. Complete histopathologic examinations were performed on all control rats and mice, 20000-ppm rats and 10000-ppm mice. In addition to gross lesions, tissue masses and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, oesophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon and rectum), liver, lung, lymph nodes (mandibular or mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial or clitoral gland (rats), prostate gland, salivary gland, skin, small intestine, (duodenum, jejunum and ileum), spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder and uterus. The kidney and urinary bladder of all other rats and mice were also examined.

**RESULTS**

- **NOEL (rats):** 1250 ppm
- **LOEL (rats):** 2500 ppm
- **NOEL (mice):** 625 ppm (males), not achieved for females
- **LOEL (mice):** 1250 ppm (males), 625 ppm (females)

- **Actual dose received by sex:**
  Rats - 100, 200, 400, 800, 1700 mg/kg bw (male), 100, 200, 400, 800, 1630 mg/kg (female)
  Mice – 100, 200, 500, 1300, 3000 mg/kg bw (male), 140, 300, 600, 1200, 2900 mg/kg bw (female)

- Toxic response/effects by dose level:

- Statistical results, as appropriate:

**Remarks:**

- **Body weight:**
  Rats – The final mean body weights and weight gains of 5000, 10000 and 20000-ppm males and females were significantly lower than those of the controls.
  Mice – The final mean body weights and body weight gains of males and females receiving 1250, 2500, 5000 or 10000-ppm and of females receiving 625 ppm were significantly lower than those of the controls.

- **Food/water consumption:**
  Rats – Feed consumption by exposed animals was lower than that by controls at week 1, but was generally similar to or slightly higher than that of controls at week 13.
  Mice – Feed consumption by exposed mice was generally higher than that by controls throughout the study.

- **Description, severity, time of onset and duration of clinical signs:**
  Rats – No chemical-related clinical findings were observed.
  Mice – Clinical findings included abnormal posture and hypoactivity in 10000-ppm male and female mice.

- **Ophthalmologic findings, incidence and severity:** No data

- **Hematologic findings, incidence and severity:** No data

- **Clinical biochemistry findings, incidence and severity:**
  Rats – Serum protein and albumin concentrations in female rats exposed to 2500 ppm and higher were slightly lower than controls.
  Mice – Blood urea nitrogen concentrations of 5000-ppm females and 10000-ppm males and females were greater than controls.

- **Urinalysis:**
  Rats – At the end of the study, 16 hour urine volumes in 10000 and 20000-ppm male rats were two-fold greater than controls. Urine specific gravity was lower than controls in 5000, 10000 and 20000-ppm males.
  Mice – Decreased urine specific gravity occurred in 10000-ppm females.

- **Mortality and time to death:**
  Rats – no animals died during the study
  Mice – one female (control), 2 males & 1 female (625 ppm), 1 female (1250 ppm), 1 female (2500 ppm), 1 female (5000 ppm), 3 males (10000 ppm) died during the study.

- **Gross pathology incidence and severity:**
  Rats – There were no treatment-related gross lesions.

Mice - There were no treatment-related gross lesions.

- **Organ weight changes:**
  Rats – No biologically significant differences in organ weights were observed
  Mice – The absolute and relative weights of several organs in 5000 and 10000-ppm animals were lower than those in the control group. These findings were attributed to the low body weights in these groups. In males exposed to 5000 or 10000 ppm, weights of the right cauda and right epididymis were significantly lower than those of control males and decreased with increasing exposure level.

- **Histopathology incidence and severity:**
  Rats – A minimal to mild degeneration of the renal papilla was present in 5000, 10000 and 20000-ppm male rats and in one female rat in the 20000 ppm group. Minimal hyperplasia of the transitional epithelium of the urinary bladder was present in 20000-ppm males.
  Mice – There was an exposure and treatment-related increase in the incidence of papillary necrosis. In the cortex of the kidney, there were foci of renal tubule regeneration and fibrosis. These lesions were present in 2500, 5000 and 10000-ppm males and 10000-ppm females. Mild urinary bladder hyperplasia of the transitional epithelium was observed in 5000 and 10000-ppm males and females. In 7/9 female mice from the 10000-ppm group there was also a minimal inflammatory cell infiltration in the urinary bladder mucosa and focal necrosis of the transitional cell epithelium.

Incidence of selected non-neoplastic lesions in rats

| | Dose (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 1250 | 2500 | 5000 | 10000 | 20000 |
| **Male** | | | | | | |
| Kidney [a] | 10 | 10 | 10 | 10 | 10 | 10 |
| Degeneration, Papillary [b] | 0 | 0 | 0 | 3 (1.0)[c] | 6** (1.3) | 8** (1.3) |
| | | | | | | |
| Urinary Bladder | 10 | 10 | 10 | 10 | 10 | 10 |
| Hyperplasia | 0 | 0 | 0 | 0 | 0 | 9** (1.0) |
| | | | | | | |
| **Female** | | | | | | |
| Kidney | 10 | 10 | 10 | 10 | 10 | 10 |
| Degeneration, Papillary | 0 | 0 | 0 | 0 | 0 | 1 (1.0) |

** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test. [a] Number of animals with organ examined microscopically. [b] Number of animals with lesion. [c] Average severity grade of lesions in affected rats: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Incidence of selected non-neoplastic lesions in mice

| | Dose (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 625 | 1250 | 2500 | 5000 | 10000 |
| **Male** | | | | | | |
| Kidney [a] | 10 | 10 | 10 | 10 | 10 | 10 |
| Necrosis, Papillary [b] | 0 | 0 | 0 | 5* (1.2)[c] | 4* (1.5) | 9** (2.2) |
| Regeneration, Renal Tubule | 0 | 0 | 0 | 4* (1.3) | 4* (1.5) | 7** (2.3) |
| Fibrosis | 0 | 0 | 0 | 4* (1.3) | 2 (1.5) | 7** (2.1) |
| | | | | | | |
| Urinary Bladder | 10 | 10 | 10 | 10 | 10 | 8 |
| Hyperplasia | 0 | 0 | 0 | 0 | 4* (1.0) | 7** (2.0) |
| | | | | | | |
| **Female** | | | | | | |
| Kidney | 10 | 10 | 10 | 10 | 10 | 10 |
| Necrosis, Papillary | 0 | 0 | 0 | 0 | 0 | 2 (1.0) |
| Regeneration, Renal Tubule | 0 | 0 | 0 | 0 | 0 | 4* (1.8) |
| Fibrosis | 0 | 0 | 0 | 0 | 0 | 2 (1.5) |
| | | | | | | |
| Urinary Bladder | 10 | 10 | 10 | 10 | 10 | 10 |
| Hyperplasia | 0 | 0 | 0 | 0 | 10** (2.0) | 9** (1.6) |

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test. ** $P \leq 0.01$. [a] Number of animals with organ examined microscopically. [b] Number of animals with lesion. [c] Average severity grade of lesions in affected mice: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.

**CONCLUSIONS**

**Remarks:**
Rats: Based on lower final mean body weights in the 20000-ppm males and females, the incidences of renal papillary degeneration in 20000-ppm males and females, and hyperplasia of the urinary bladder in 20000-ppm males, the high dose selected for continuous exposure in the 2-year study was 10000 ppm.

Mice: Based on lower final mean body weights and organ weights in 5000 and 10000-ppm males and females and the presence of kidney (papillary necrosis) and urinary bladder lesions in 2500, 5000 and 10000-ppm males and females, the high dose selected for the 2-year study was 1250 ppm.

**DATA QUALITY**

- 1, Valid without restrictions

**Remarks:** Well-conducted study performed by American Biogenics Corporation.

**REFERENCES:**
NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2,2-bis(bromomethyl)-1,3-propanediol (FR-1138, CAS No. 3296-90-0) in F344/N Rats and B6C3F1 Mice (Feed Studies), NTP TR 452, National Toxicology Program, May 1996

**OTHER:**

- **Last Changed:** October 4 2002
- **Order number for sorting:** 2

**Remarks:**

## HUMAN HEALTH ENDPOINTS
## 16.3 REPEATED DOSE TOXICITY

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dow Chemical Company, FR -1138. Purity: approximately 80%, Identity of impurities: monobromoneopentyl triol (6%), tribromoneopentyl alcohol (8%), others (3%)

**METHOD**

- **Method/guideline followed:** Similar to OECD 453.
- **Test type:** 2 year repeated dose toxicity and carcinogenicity study
- **GLP:** No data
- **Year:** 1979
- **Species:** Rat
- **Strain:** Sprague-Dawley
- **Route of administration:** Oral feed
- **Duration of test:** 2 years
- **Doses/concentration levels:** 0, 5, 100 mg/kg/day
- **Sex:** Male/female
- **Exposure period:** 2 years
- **Frequency of treatment:** Continuous
- **Control group and treatment:** Male/female, 49-50/sex + 5/sex for one year interim kill + 10/sex for tissue analysis
- **Post exposure observation period:** none
- **Statistical methods:** Food consumption, hematology, urinary & clinical chemistry parameters, body & organ weights and organ/body weight ratio data were analyzed by a one-way analysis of variance followed by Dunnett's test (preceded by the sequential outlier's test for food consumption). Data on mortality, palpable masses, gross pathology, histopathology and tumor incidences were analyzed using Fisher's Exact Probability test.

**Remarks:**

- **Test subjects**
  - **Age at study initiation:** 8-9 weeks

- **No. of animals/sex/dose:** 49-50/sex/dose

- **Study Design**

  - **Vehicle:** Feed

  - **Satellite groups and reasons they were added:** 5/sex/group for 1 year interim kill + 10/sex/group for tissue analysis

  - **Clinical observations performed and frequency:** General health status and possible toxicological response monitored at least weekly during year 1 and almost daily during year 2. Hematological determinations conducted after 90-91 days and 356-357 days of treatment. Additional blood samples collected after 713-714 days and 725 and 731 days (female only). Urine samples collected after 90-91, 356-357 and 713-714 days of treatment. Clinical chemistry parameters were monitored after 94 days, 1 year and 2 years.

  - **Organs examined at necropsy (macroscopic and microscopic):** Year 1 evaluation: Eyes, liver, kidneys, heart, pancreas, spleen, brain, vertebrae with spinal cord, peripheral (sciatic) nerve, pituitary gland, stomach, small intestine, large intestine, cecum, mesenteric lymph node(s), skeletal (thigh) muscle, salivary gland, testes, epididymides, accessory male sex glands, urinary bladder, uretus, ovary trachea, esophagus, aorta, thoracic lymph node(s), thymus, lungs, integument, thyroid gland, parathyroid glands, adipose tissue, adrenal gland(s), sternum, tongue, mandible and any other grossly observed lesion. The weights of the liver, kidneys, brain, heart and testes (males) were also recorded. Year 2 evaluation: As Year 1, plus femoral bone marrow smear from all female rats.

**RESULTS**

- **NOAEL:** 5 mg/kg/day
- **LOAEL:** 100 mg/kg/day
- **Actual dose received by sex:** The concentration of the test material was adjusted on a weekly basis for the first 3 months, and quarterly thereafter to maintain the designated dose levels on a mg/kg bw/day basis. The results of 8 different analyses conducted on samples collected during months 5, 8, 13, 17, 18, 19, 20 and 22 indicated the following analytical content of test material (expressed as percent of nominal concentrations):

| Control | Group | None detected |
|---|---|---|
| 5 mg/kg/day | Female | 95.5±24.7% |
| 5 mg/kg/day | Male | 113±46.0% |
| 100 mg/kg/day | Female | 97.8±7.2% |
| 100 mg/kg/day | Male | 97.8±4.4% |

- Toxic response/effects by dose level:

- Statistical results, as appropriate:

**Remarks:**

- **Body weight:** No toxicologically significant differences in body weight were detected.

- **Food/water consumption:** No consistent deviations in food consumption of males or females at either of the 2 dose levels during the study.

- **Description, severity, time of onset and duration of clinical signs:** None

- **Ophthalmologic findings, incidence and severity:** No data

- **Hematologic findings, incidence and severity:** No toxicologically significant differences between controls and treatment groups.

- **Clinical biochemistry findings, incidence and severity:** No toxicologically significant differences between controls and treatment groups.

- **Mortality and time to death:** Male rats given 5 or 100 mg/kg/day showed no differences in mortality compared to that of the control group. Female rats receiving 100 mg/kg/day had statistically increased mortality rates for months 16 and 17, but this was considered to be of questionable toxicological significance.

- **Gross pathology incidence and severity:** Six of eleven female rats given 100 mg/kg/day showed bilateral diffuse opacity of the lenses. This was not noted in the controls or the group of females given 5 mg/kg/day.

- **Organ weight changes:** Male rats given 100 mg/kg/day killed after 1 year of treatment showed a statistically significant increase in relative liver weights. This was the only toxicologically significant difference between controls and treatment groups.

- **Histopathology incidence and severity:** Statistical increase in the incidence of thyroid retention cyst formation in 100 mg/kg/day male rats, which may or may not have been treatment-related. Female rats given 100 mg/kg/day showed six of eleven rats with bilateral lenticular degeneration of the anterior cortex graded as moderate in degree. In addition, some of the rats showed bilateral degeneration of the posterior cortex and basophilic staining material within this region of the lens. There were several observations noted on examination of the livers of female rats given 100 mg/kg/day that were considered to be related to treatment. These included hepatocellular degenerative changes consisting of increased eosinophilic cytoplasmic homogeneity accompanied by a slight increase in the incidence of livers having several foci or a single area of hepatocellular alteration. The trend towards a slight increased incidence of individual hepatocellular necrosis noted in this group may or may not have been the result of treatment.

  Statistical analysis of the incidence of tumors found at necropsy showed there were no significant differences between control and treatment groups.

**CONCLUSIONS**

**Remarks:**

**DATA QUALITY**

- 2, Valid with restrictions

**Remarks:** Appears to be a well conducted study, but no GLP information.

**REFERENCES:**

Keyes, D.G., et al, Results of a two year toxicity and onconogenic study of rats ingesting diets containing dibromoneopentyl glycol (FR-1138), J. Combustion Toxicology, 7, p77, 1980

**OTHER:**

- **Last Changed:** October 4 2002
- **Order number for sorting:** 3

**Remarks:**

## HUMAN HEALTH ENDPOINTS
## 17. TOXICITY TO REPRODUCTION

**TEST SUBSTANCE**

- 2,2-bis(bromomethyl)-1,3-propanediol (CAS No. 3296-90-0)

**Remarks:** Source: Dow Chemical Company, Lot No.: MM05137-636, Purity: approx 87.3%, Identity of impurities: 2,2-bis (hydroxymethyl)-1-bromo-3-hydroxypropane (6.7%), 2,2-bis (bromom ethyl)-1-bromo-3-hydroxypropane (5.5%), 3,3-bis (bromomethyl) oxetane (0.5%), water (0.3±0.1%).

**METHOD**

- **Method/guideline:** The study was performed using the NTP Fertility Assessment by Continuous Breeding (FACB) system. It consists of four related tasks as follows: Task 1, dose finding; Task 2, continuous breeding phase; Task 3, identification of the affected sex; and Task 4, offspring assessment. Task 1 is conducted to determine suitable doses for the cohabitation study. The test chemical is administered for 14 consecutive days and the maximum tolerated dose (MTD) is estimated. Task 2 is designed to determine the effect of the estimated MTD and two lower dose levels on fertility and reproduction. In this phase, treatment is continued for 18 weeks. Task 3 (a crossover mating trial) is conducted using males and females from the control and high dose groups to determine whether the male, female or both sexes are affected. Task 4 is designed to evaluate reproductive performance in offspring (second generation) from the final Task 2 litters.

- **Type:** Two generation

- **GLP:** Yes

- **Year:** 1986

- **Species:** Mouse

- **Strain:** CD-1 (ICR) BR

- **Route of administration:** Oral feed

- **Doses/concentration levels:** Range Finding Study (Task 1): 0, 0.025, 0.05, 0.1, 0.25, 0.5 % w/w
  Cohabitation Study (Task 2): 0, 0.1, 0.2, 0.4 %w/w
  Crossover Mating Study (Task 3): No chemical treatment during the mating period. 0, 0.4 %w/w during post-mating holding period.
  Second Generation Study (Task 4): 0, 0.1, 0.2, 0.4 %w/w

- **Sex:** Male/female

- **Control group:** Range Finding Study (Task 1): 8 males, 8 females; vehicle control
  Parental (Task 2): 40 males, 40 females; vehicle control
  Crossover Mating Study (Task 3): 20 males, 20 females; vehicle control
  Second Generation Study (Task 4): 20 males, 20 females; vehicle control

- **Frequency of treatment:** Daily, ad libitum

- **Duration of test:** Range Finding Study (Task 1): 2 weeks
  Cohabitation Study (Task 2): 1 week pre-treatment, 14 weeks cohabitation, and 3 weeks holding period
  Crossover Mating Study (Task 3): 1 week cohabitation (maximum), and 3 weeks holding period
  Second Generation Study (Task 4): 74±10 days premating, 7 days (maximum cohabitation), and 3 weeks holding period

- **Premating exposure period for males:** Parental (Task 2): 7 days

F1 (Task 4): 64-84 days

- **Premating exposure period for females:** Parental (Task 2): 7 days
  F1 (Task 4): 64-84 days

- **Statistical methods:** The Cochran-Armitage test was used in Task 2 to assess dose-related trends in fertility. Days between litters were evaluated by Shirley's test. In Task 3 a $\chi^2$ test for homogeneity was used to test for an overall difference in fertility among the cross-mated groups. Pairwise comparisons between control and dosed groups were determined by the Fisher's exact test. Dose group means for the proportion of live pups and sex ratio of pups were tested for overall differences by the Kruskal-Wallis test and for ordered differences by the Jonckheere test. Pairwise comparisons of treatment group means were determined by the Wilcoxon-Mann-Whitney *U* test. Differences in average pup weight were investigated using analysis of covariance (ANCOVA), using avaerage litter size inclusive of live and dead pups as covariant. Pairwise comparisons were performed using a two-tailed *t* test. For organ weights, analysis of covariance was performed to determine least squares treatment group means, which were then tested for overall and pairwise equality by two-sided *F* and *t* tests, respectively. The Kruskal-Wallis and Wilcoxon-Mann-Whitney *U* tests were also employed in the analysis of unadjusted body and organ weights.

**Remarks:**

- **Test animals**

  - **Parental:** 20 male, 20 female per dose. Age: 11 weeks
  - **F1:** 20 male, 20 female per dose. Age: 64-84 days

- **Test design**

  - **Vehicle:** Substance was administered in feed.

  - **Dosing schedules and pre and post dosing observations periods:**

    **Parental (Task 2):** Animals fed daily ad libitum for 7 days prior to mating followed by 14 weeks after initial mating and a further 3 week observation period.
    **F1 (Task 4):** Animals received the substance initially through lactation for 3 weeks until weaning, then fed daily ad libitum until mating at 74±10 days, then for a further 7 days. All animals were necropsied at the end of this period.

- **Mating procedures:** Task 2: 1 male and 1 female per cage. Cohabitation for 14 weeks.
  Task 3: 1 male and 1 female per cage. Cohabitation until vaginal plug was detected or for a maximum of 7 days.
  Task 4: 1 male and 1 female per cage. Cohabitation continued for seven days or until a copulatory plug was found.

- **Standardization of litters:** No

- **Parameters assessed during study P and F1 as appropriate:**

  - **Clinical observations performed and frequency:** Task 2 parental body weights were measured on days –7 (start of dosing), 0 (start of cohabitation), 7, 28, 56, 84 and 112.

    F1 animals (Task 4) were weighed at weaning, the first day of cohabitation and once a week thereafter.

  - **Estrous cycle length and pattern (number of days spent in each phase):** Studied during Task 3 (Parental) and Task 4 (F1).

  - **Sperm examination:** Sperm motility, sperm counts per 'g' caudal tissue, and the incidence of abnormal sperm were examined at the end of Task 3 (parental) and Task 4 (F1)

- **Parameters assessed during study F1 and F2 as appropriate:**

- **Clinical observations performed and frequency:** At least twice per day: Loss of hair, diarrhoea, wounds, hyperactivity, inactivity, tearing or ocular discharge, paralysis, nasal discharge, blood in cage and/or on animal, abnormal posture or death.

- **Others, for example anogenital distance, if performed:** Anogenital distance was used to sex pups

- **Organs examined at necropsy (macroscopic and microscopic):** Female – liver, kidney, lymph nodes, mammary glands, ovary, oviduct, uterus, vagina, urinary bladder and skeletal muscle; Male – kidney, liver, epididymis, prostate gland, seminal vesicles, skin, testes and urinary bladder.

**RESULTS**

- **F0 NOEL:** 0.1% adults, 0.1% offspring
- **F1 NOEL:** 0.1% adults, 0.1% offspring

- **Actual dose received by dose level by sex:** Male mice in the 0.1, 0.2 and 0.4% dose groups received approximately 141, 274 and 589 mg/kg bw/day. Female dose was not calculated.

- **Parental data and F1 as appropriate (toxic response/effects with NOAEL value). Provide at a minimum qualitative descriptions of elements where dose related observations were seen:** Refer to Remarks

- **Offspring toxicity F1 and F2 as appropriate (toxic response/effects with NOAEL value). Provide, at a minimum, qualitative descriptions of elements where dose related observations were seen:** Refer to Remarks

- **Statistical results, as appropriate:** Refer to Remarks

**Remarks:**

- **Parental data and F1 as appropriate, provide at a minimum qualitative descriptions of elements where dose related observations were seen:**

- **Body weight:** Parental (Task 2): The average body weights of male and female mice in the 0.4% dose groups were significantly lower ($p<0.05$) than the control groups from week 2 onwards (apart from females at week 14), as shown in the table below.

| Treatment Group | | Body Weight (g) Group Mean±SE | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Week 1 | Week 2 | Week 3 | Week 6 | Week 10 | Week 14 | Week 18 |
| Control (0.0 mg/g) | M | 33.6±0.30 (40)[a] | 35.7±0.32 (40) | 34.6±0.29 (40) | 35.3±0.30 (40) | 36.6±0.35 (40) | 37.5±0.38 (40) | 38.2±0.44 (39)[b] |
| | F | 26.2±0.22 (40) | 28.0±0.24 (40) | 30.5±0.24 (40) | 34.6±0.39 (40) | 49.4±1.01 (40) | 40.7±1.16 (40) | 45.0±1.02 (40) |
| 0.1% (1.0 mg/g) | M | 33.9±0.51 (20) | 35.1±0.49 (20) | 34.1±0.48 (20) | 35.0±0.59 (20) | 36.4±0.73 (20) | 37.2±0.83 (20) | -[c] |
| | F | 26.0±0.34 (20) | 27.1±0.30 (20) | 30.2±0.39 (20) | 33.7±0.58 (20) | 48.1±1.85 (20) | 38.6±1.10 (20) | 42.0±1.19 (20) |
| 0.2% (2.0 mg/g) | M | 34.1±0.37 (20) | 35.4±0.39 (20) | 34.3±0.38(20) | 35.0±0.59 (20) | 36.4±0.81 (20) | 36.9±0.94 (20) | -[c] |
| | F | 25.8±0.38 (20) | 27.1±0.36 (20) | 29.3±0.35 (20)[d] | 32.8±0.37 (20)[d] | 45.7±1.37 (19)[e] | 37.6±1.09 (19) | 41.0±1.20 (17)[d,f] |
| 0.4% (4.0 mg/g) | M | 34.0±0.35 (20) | 33.7±0.42 (20)[d] | 32.5±0.33 (20)[d] | 32.5±0.42 (20)[d] | 33.1±0.48 (20)[d] | 34.1±0.60 (20)[d] | 34.3±0.71 (20)[d] |
| | F | 25.9±0.42 (20) | 27.0±0.36 (20)[d] | 28.4±0.39 (20)[d] | 30.2±0.94 (20)[d] | 33.7±1.18 (20)[d] | 36.6±1.69 (19)[g] | 34.7±1.40 (19)[d] |

[a] Number of animals providing the data indicated in parenthesis. [b] One male was sacrificed during week 16 of the study as per instructions of the veterinarian in charge. [c] animals were sacrificed during week 16 of the study. [d] Significantly different ($p<0.05$) from the control group. [e] One female died during week 7 of the study. [f] One female died during week 17 of the study and 1 female was sacrificed during week 17 of the study as per instructions of the veterinarian in charge. [g] One female died during week 11 of the study

Parental (Task 3): The body weights of both males and females from the 0.4% groups were significantly lower than the animals in the control group throughout the 4-week study, as shown in the table below:

| Treatment Group | | Body Weight (g) Group Mean±SE | | | |
|---|---|---|---|---|---|
| | | Week 22 | Week 23 | Week 24 | Week 25 |
| Control | M | 40.9±0.49 (39)[a] | 38.7±0.47 (39) | 39.3±0.48 (39) | 38.7±0.51 (39) |
| (0.0 mg/g) | F | 37.6±0.43 (40) | 37.7±0.50 (40) | 43.2±0.81 (40) | 46.4±1.65 (40) |
| 0.4% | M | 35.3±0.88 (20)[b] | 34.4±0.72 (20)[b] | 34.1±0.83 (20)[b] | 33.8±0.90 (20)[b] |
| (4.0 mg/g) | F | 31.0±0.60 (18)[b] | 31.7±0.61 (18)[b] | 33.7±0.81 (18)[b] | 38.4±1.61 (18)[b] |

[a] Number of animals providing the data indicated in parenthesis. [b] Significantly different ($p<0.05$) from the control group

F1 (Task 4): Pups in the 3 dose groups were smaller than the control group at weaning as well as through maturation. As shown in the table below, this difference was significant for both males and females in the 0.4% dose groups at all time intervals.

| Treatment Group | | Body Weight (g) Group Mean±SE | | | | |
|---|---|---|---|---|---|---|
| | | Week 19-21[a] | Week 28 | Week 29 | Week 30 | Week 31 |
| Control | M | 11.9±0.49 (20)[b] | 33.9±0.59 (20) | 34.0±0.60 (20) | 35.4±0.64 (20) | 36.4±0.66 (20) |
| (0.0 mg/g) | F | 11.4±0.44 (40) | 26.6±0.56 (19)[c] | 30.0±0.64 (20) | 37.5±0.82 (20) | 43.7±2.85 (20) |
| 0.1% | M | 10.2±0.40 (20)[d] | 32.8±0.62 (20) | 33.3±0.52 (20) | 33.6±0.55 (20)[d] | 34.6±0.56 (20)[d] |
| (1.0 mg/g) | F | 9.9±0.39 (20)[d] | 24.5±0.41 (20)[d] | 28.5±0.40 (20) | 34.8±0.64 (20)[d] | 41.6±2.58 (20) |
| 0.2% | M | 10.5±0.45 (20)[d] | 31.5±0.62 (20)[d] | 31.7±0.59(20)[d] | 32.4±0.61 (20)[d] | 33.1±0.60 (20)[d] |
| (2.0 mg/g) | F | 10.2±0.43 (20) | 24.5±0.50 (20)[d] | 28.3±0.58 (20) | 33.8±0.91 (20)[d] | 40.7±2.67 (19) |
| 0.4% | M | 9.0±0.53 (20)[d] | 25.5±0.59 (20)[d] | 26.2±0.56 (20)[d] | 26.3±0.67 (20)[d] | 26.9±0.80 (20)[d] |
| (4.0 mg/g) | F | 8.8±0.47 (20)[d] | 21.7±0.37 (20)[d] | 24.3±0.39 (20)[d] | 28.5±0.70 (20)[d] | 32.1±1.77 (20)[d] |

[a] Represents average pup weight at weaning; pups were weaned during weeks 19 to 21 of the study. [b] Number of animals providing the data indicated in parenthesis. [c] Due to technical error, one female mouse was not weighed during week 28. [d] Significantly different ($p<0.05$) from the control group.

- **Food/water consumption:** There were no statistically significant differences in the average daily consumption of control/dose feed by animals in the control and treatment groups (parental or F1) in this study.

- **Description, severity, time of onset and duration of clinical signs:** None

- **Fertility index:** There was no significant difference in the fertility index values between control and dose group animals during Task 2 (Parental) or between control and dose group animals during Task 4 (F1). The fertility index of the control male x 0.4% dose females was significantly different ($p<0.01$) from the control male x control female group in Task 3 (Parental). The data are presented in the tables below.

Fertility of Pairs during Continuous Breeding (Parental, Task 2)

| Treatment group | No. Fertile/No. Cohabited | Fertility Index (%)[a] |
|---|---|---|
| Control | 39/40 | 97 |
| 0.1% | 19/20 | 95 |
| 0.2% | 19/19[b] | 100 |
| 0.4% | 19/19[c] | 100 |

[a] Fertility Index (%) = 100 x No. Fertile/No. Cohabited. [b] One female died during week 7 of the study; data were excluded. [c] One female died during week 11 of the study; data were excluded

Mating and fertility of Pairs after a Mating trial to determine the Affected Sex (Parental, Task 3)

| Treatment group | No. with Copulatory Plugs/ No. Cohabited | Mating Index (%)[a] | No. Fertile/ No. Cohabited | Fertility Index (%)[b] |
|---|---|---|---|---|
| Control Male x Control Female | 19/20[c] | 95 | 17/20 | 85 |
| Control Male x 0.4% Female | 17/18 | 94 | 6/18 | 33[d] |
| 0.4% Male x Control Female | 17/20 | 85 | 16/20 | 80 |

[a] Mating Index (%) = 100 x No. with Copulatory Plugs/No. Cohabited. [b] Fertility Index (%) = 100 x No. Fertile/No. Cohabited. [c] Although not detected by direct means, 2 females were scored copulatory plug-positive based on delivery of litters. [d] Significantly different ($p<0.01$) from the control male x control female group.

Reproductive Performance (F1, Task 4)

| Treatment | No. with Copulatory Plugs/ | Mating Index | No. Fertile/ | Fertility Index |
|---|---|---|---|---|

| group | No. Cohabited | (%)[a] | No. Cohabited | (%)[b] |
|---|---|---|---|---|
| Control | 20/20 | 100 | 19/20 | 95 |
| 0.1% | 20/20[c] | 100 | 18/20 | 90 |
| 0.2% | 20/20 | 100 | 18/20 | 90 |
| 0.4% | 20/20 | 100 | 18/20 | 90 |

[a] Mating Index (%) = 100 x No. with Copulatory Plugs/No. Cohabited. [b] Fertility Index (%) = 100 x No. Fertile/No. Cohabited
[c] Although not detected by direct means, 2 females were scored copulatory plug-positive based on delivery of litters.

- **Precoital interval (with number of days until mating and number of estrous periods until mating):** No data

- **Duration of gestation (calculated from day 0 of pregnancy):** The number of days to litter for the 0.4% dose group was significantly increased over control group values for the first four litters. It was also noted that there was a decrease in dams delivering fourth and fifth litters in the 0.4% treatment group.

Days to Litter (Task 2)

| Treatment Group | Days to litter | | | | |
|---|---|---|---|---|---|
| | Litter 1 | Litter 2 | Litter 3 | Litter 4 | Litter 5 |
| Control | 20.62±0.17 (39)[a] | 20.13±0.23 (39) | 20.28±0.14 (39) | 20.13±0.08 (39) | 20.58±0.37 (38) |
| 0.1% | 20.47±0.32 (19) | 20.32±0.61 (19) | 20.42±0.27 (19) | 20.11±0.13 (10) | 20.00±0.08 (19) |
| 0.2% | 21.30±0.46 (20) | 19.85±0.13 (20) | 20.32±0.11 (19) | 20.84±0.41 (19) | 20.67±0.44 (18) |
| 0.4% | 26.70±2.40 (20)* | 27.80±3.35 (20)* | 22.74±1.45 (19)* | 22.06±1.21 (16)[b,*] | 20.73±0.19 (11) |

[a] All data are expressed as means±SE, with the number of dams producing litters in parenthesis. [b] One female died during Week 11 of the study. * Denotes significantly different from the control ($p<0.05$)

- **Gestation index (live litters/pregnancies):** No data

- **Change in lactation:** No data

- **Changes in estrous cycles:** A detailed vaginal cytology evaluation was undertaken at the end of Task 3 (Parental). The average estrous cycle length in the treated animals was 4.9 days vs. a control value of 4.7 days. Treatment with the test substance had no apparent effect on estrual cyclicity.

Summary of Data from Vaginal Cytology Studies (Parental, Task 3)

| Treatment group | Terminal Body Weight (g) Group Mean±SE | Relative Frequency of Estrous Stages | | | | | Estrous Cycle Length (days) Group Mean±SE |
|---|---|---|---|---|---|---|---|
| | | %P | %E | %M | %D | %NC | |
| Control | 38.0±0.56 (38)[a,b] | 13.0 (39) | 20.0 (39) | 23.0 (39) | 44.1 (39)[c] | 0.0 (39) | 4.69±0.12 (26)[b,d] |
| 0.4% | 31.4±0.62 (17)[e] | 18.5 (17) | 22.7 (17) | 22.7 (17) | 36.1 (17)[f] | 0.0 (17) | 4.93±0.20 (14)[g] |

[a] Number of animals providing the data indicated in parenthesis. [b] In the control group, 1 mouse was found dead on day 5 of vaginal smearing. Data from 4 days of vaginal smears are included. [c] For 7 consecutive days, 3 animals in the control group remained in diestrus stage. [d] In 12 out of the 39 animals in the control group, estrous cycle length was 7 days or not clear. [e] Significantly different ($p<0.01$) from the control group. [f] For 7 consecutive days, 2 animals in the 0.4% dose group remained in diestrus stage. [g] In 3 out of the 17 animals in the 0.4% dose group, estrous cycle length was not clear. P = Proestrus; E = Estrus; M = Metestrus; D = Diestrus; NC = Not Clear

In the F1 study (Task 4) vaginal smears were prepared for 7 days prior to necropsy. The average estrous cycle varied between 5.0 to 5.2 days for animals in the control and 3 dose groups. Estrual cyclicity was not affected at the 0.1 and 0.2% levels but at the 0.4% level relative frequency of the diestrus phase was 43% vs. a control value of 25%.

Summary of Data from Vaginal Cytology Studies (F1, Task 4)

| Treatment group | Terminal Body Weight (g) | Relative Frequency of Estrous Stages | | | | | Estrous Cycle Length (days) |
|---|---|---|---|---|---|---|---|
| | Group Mean±SE | %P | %E | %M | %D | %NC | Group Mean±SE |
| Control | 32.2±0.71 (20)[a] | 22.1 (20) | 32.1 (20) | 20.7 (20) | 25.0 (20) | 0.0 (20) | 5.18±0.15 (17)[b] |
| 0.1% | 30.2±0.35 (20)[c] | 14.3 (20) | 34.3 (20) | 22.9 (20) | 28.6 (20) | 0.0 (20) | 4.95±0.12 (19)[d] |
| 0.2% | 30.4±0.56 (20) | 20.0 (20) | 35.0 (20) | 17.1 (20) | 27.9 (20) | 0.0 (20) | 5.21±0.14 (19)[e] |
| 0.4% | 26.5±0.41 (20)[f] | 16.4 (20) | 25.0 (20) | 15.7 (20) | 42.9 (20) | 0.0 (20) | 4.94±0.15 (18)[g] |

a Number of animals providing the data indicated in parenthesis. [b] In 3 out of the 20 animals in the control group, estrous cycle length was 7 days. [c] Significantly different ($p<0.05$) from the control group. [d] In 1 out of the 20 animals in the 0.1% dose group, estrous cycle length was 7 days. [e] In 1 out of the 20 animals in the 0.2% dose group, estrous cycle length was not clear. [f] Significantly different ($p<0.01$) from the control group. [g] In 2 out of the 20 animals in the 0.4% dose group, estrous cycle length was 7 days or not clear. P = Proestrus; E = Estrus; M = Metestrus; D = Diestrus; NC = Not Clear

- **Effects on sperm:** Sperm assessment studies following Task 3 (Parental) showed that treatment with the test substance had no significant effect ($p>0.05$) on sperm motility, sperm counts per 'g' caudal tissue, or the incidence of abnormal sperm (see below).

Summary of Data from Sperm Studies (Parental, Task 3)

| Treatment group | Weight | | | | Sperm Motility (%) | Sperm Density x $10^{6}$ [a] | Abnormal Sperm (%) |
|---|---|---|---|---|---|---|---|
| | Body (g) | R. Caudal (mg) | R. Epididymal (mg) | R. Testicular (g) | | | |
| Control | 40.65 ±0.52 (39)[b,c] | 19.564±0.300 (39) | 53.515±0.737 (39) | 0.140±0.004 (39) | 94.05±0.40 (39) | 1102±46 (39) | 3.07±0.36 (39) |
| 0.4% | 35.67±1.01 (19)[d,f] | 17.705±0.645 (19)[e] | 50.500±1.217 (19) | 0.138±0.004 (19) | 94.12±0.80 (19) | 1076±42 (19) | 2.92±0.24 (19) |

[a] Per g caudal tissue. [b] Number of animals providing the data indicated in parenthesis. [c] Mean±SE. [d] Significantly different ($p<0.01$) from the control group. [e] Significantly different ($p<0.05$) from the control group. [f] Severe internal infection noted at necropsy for 1 mouse: all data were excluded

Sperm assessment studies following Task 4 (F1) showed that treatment with the test substance at up to 0.4% dose level has no significant effect ($p>0.05$) on sperm motility or the incidence of abnormal sperm in the second generation CD-1 mice. The sperm density was reduced by approximately 14% in the 0.4% dose group (see below).

Summary of Data from Sperm Studies (F1, Task 4)

| Treatment group | Weight | | | | Sperm Motility (%) | Sperm Density x $10^{6}$ [a] | Abnormal Sperm (%) |
|---|---|---|---|---|---|---|---|
| | Body (g) | R. Caudal (mg) | R. Epididymal (mg) | R. Testicular (g) | | | |
| Control | 37.57±0.71 (20)[b,c] | 18.850±0.696 (20) | 49.040±1.518 (20) | 0.140±0.004 (20) | 88.6±2.95 (20) | 1307±66 (20) | 3.31±0.49 (20) |
| 0.1% | 35.73±0.64 (20) | 18.820±0.411 (20) | 49.740±1.481 (20) | 0.139±0.005 (20) | 93.1±0.90 (20) | 1427±49 (20) | 3.28±0.43 (20) |
| 0.2% | 34.37±0.61 (20)[d] | 18.550±0.594 (20) | 47.800±1.107 (20) | 0.139±0.005 (20) | 92.3±0.98 (20) | 1400±91 (20) | 2.56±0.43 (20) |
| 0.4% | 28.24±0.87 (20)[d] | 14.530±0.622 (20)[d] | 39.230±1.413 (20)[d] | 0.117±0.004 (20)[d] | 91.9±0.91 (20) | 1124±76 (20)[e] | 3.70±0.59 (20) |

[a] Per g caudal tissue. [b] Number of animals providing the data indicated in parenthesis. [c] Mean±SE. [d] Significantly different ($p<0.01$) from the control group. [e] Significantly different ($p<0.05$) from the control group

- **Hematological findings incidence and severity:** No data
- **Clinical biochemistry findings incidence and severity:** No data
- **Mortality:** Task 2: Two females (0.2% dose group) died during weeks 7 & 17 and other female from this group was sacrificed during week 17. One female (0.4% dose group) died during week 11.
- **Gross pathology incidence and severity:** No data
- **Clinical biochemistry findings incidence and severity:** No data
- **Number of implantations:** No data
- **Number of corpora lutea (recommended):** No data

- **Ovarian primordial follicle counts:** No data

- **Organ weight changes:** For parental animals necropsied at the end of Task 3, the group mean whole body, liver and kidney weights of female mice in the 0.4% dose group were significantly lower ($p<0.05$) than the corresponding control values. The reduction was no longer apparent when organ weights were adjusted for body weight at necropsy. For males in the 0.4% dose group, whole body, kidney, seminal vesicles and right caudal weights were significantly lower ($p<0.05$) than the corresponding control values. These differences were not apparent when organ weights were adjusted for body weight at necropsy.

- **Histopathology incidence and severity:** For parental animals necropsied at the end of Task 3, significant gross lesions were seen in the kidneys of males and females treated with the substance. Pathologic examination revealed significantly increased incidence of glomerular atrophy, degeneration, dilation, and regeneration of tubules, renal papillary necrosis, interstitial nephritis, and mineralisation in animals treated with the substance.

  A detailed histopathologic examination of F1 mice at the end of Task 4 revealed significant treatment-related gross lesions in the female mice. Changes were also observed in the kidney of many on the male animals from the 0.2 and 0.4% dose groups.

- **Offspring toxicity F1 and F2, as appropriate, provide as a minimum qualitative descriptions of elements where dose related observations were seen:**

- **Litter size and weights, sex and sex ratios:** In the continuous breeding study (Task 2) there was a significant decrease ($p<0.01$) in the mean number of litters per fertile pair at the 0.4% dose level. Other reproductive parameters affected ($p<0.01$) at this dose level were the total number of live pups per litter, the proportion of live pups born alive and the adjusted live pup weight. At the 0.2% dose level, both absolute (except for female pups) and adjusted live pup weights were significantly decreased ($p<0.05$).

Reproductive Performance of Fertile Pairs During Continuous Breeding (Parental, Task 2)

| Reproductive Parameter [a] | Treatment Group | | | |
|---|---|---|---|---|
| | Control | 0.1% | 0.2% | 0.4% |
| Litters per Pair | 4.97±0.03 (39)[b] | 5.00±0.00 (19) | 4.95±0.05 (19) | 4.37±0.21 (19)[c] |
| Live Pups per Litter | | | | |
| Male | 6.12±0.23 (39) | 6.24±0.35 (19) | 5.64±0.32 (19) | 3.47±0.27 (19)[c] |
| Female | 6.11±0.19 (39) | 6.19±0.30 (19) | 5.68±0.32 (19) | 3.34±0.30 (19)[c] |
| Combined | 12.23±0.37 (39) | 12.43±0.49 (19) | 11.32±0.59 (19) | 6.81±0.49 (19)[c] |
| Proportion of Pups Born Alive | 0.99±0.01 (39) | 0.99±0.01 (19) | 0.99±0.00 (19) | 0.97±0.01 (19)[c] |
| Sex of Pups Born Alive (Male/Total) | 0.50±0.01 (39) | 0.50±0.02 (19) | 0.50±0.01 (19) | 0.51±0.03 (19) |
| Live Pup Weight (g) | | | | |
| Male | 1.61±0.02 (39) | 1.57±0.02 (19) | 1.53±0.02 (19)[c] | 1.56±0.02 (19) |
| Female | 1.53±0.01 (39) | 1.52±0.02 (19) | 1.49±0.02 (19) | 1.53±0.02 (19) |
| Combined | 1.57±0.01 (39) | 1.55±0.02 (19) | 1.51±0.02 (19)[d] | 1.54±0.02 (19) |
| Adjusted Live Pup Weight (g)[e] | | | | |
| Male | 1.63±0.01 (39) | 1.60±0.02 (19) | 1.53±0.02 (19)[c] | 1.48±0.02 (19)[c] |
| Female | 1.56±0.01 (39) | 1.55±0.02 (19) | 1.49±0.02 (19)[c] | 1.45±0.02 (19)[c] |
| Combined | 1.59±0.01 (39) | 1.57±0.02 (19) | 1.51±0.02 (19)[c] | 1.47±0.02 (19)[c] |

[a] Mean±SE. [b] Number of fertile pairs providing the data indicated in parenthesis. [c] Significantly different ($p<0.01$) from the control group. [d] Significantly different ($p<0.05$) from the control group. [e] Least squares estimate of mean pup weight adjusted for average litter size±SE

In Task 3 (crossover study), there was a significant difference ($p<0.05$) in the number of live pups between the control male x 0.4% dose female and the 0.4% dose male x control female group. Adjusted pup weights in the former group were also significantly reduced ($p<0.05$) relative to the control male x control female group.

Reproductive Performance of Fertile Pairs after a Mating Trial to Determine Affected Sex (Parental, Task 3)

| Reproductive Parameter [a] | Treatment Group | | |
|---|---|---|---|
| | Control Male x Control Female | Control Male x 0.4% Female | 0.4% Male x Control Female |

| | | | |
|---|---|---|---|
| Live Pups per Litter | | | |
| Male | 5.00±0.39 (17)[b] | 3.17±0.75 (06)[c,d] | 5.69±0.42 (16) |
| Female | 4.71±0.80 (17) | 3.67±0.84 (06) | 5.06±0.49 (16) |
| Combined | 9.71±1.01 (17) | 6.83±1.40 (06)[d] | 10.75±0.63 (16) |
| Proportion of Pups Born Alive | 0.96±0.03 (17) | 0.91±0.07 (06) | 0.98±0.01 (16) |
| Sex of Pups Born Alive (Male/Total) | 0.53±0.05 (17) | 0.47±0.07 (06) | 0.54±0.03 (16) |
| Live Pup Weight (g) | | | |
| Male | 1.68±0.04 (16)[e] | 1.69±0.08 (06) | 1.62±0.04 (16) |
| Female | 1.60±0.05 (16)[f] | 1.58±0.05 (06) | 1.55±0.03 (16) |
| Combined | 1.66±0.04 (17) | 1.63±0.07 (06) | 1.59±0.03 (16) |
| Adjusted Live Pup Weight (g)[e] | | | |
| Male | 1.70±0.03 (16) | 1.57±0.05 (06)[c] | 1.65±0.03 (16) |
| Female | 1.61±0.03 (16) | 1.48±0.05 (06)[c] | 1.59±0.03 (16) |
| Combined | 1.66±0.02 (17) | 1.53±0.04 (06)[c] | 1.63±0.03 (16) |

[a] Mean±SE. [b:] Number of fertile pairs providing the data indicated in parenthesis. [c] Significantly different ($p<0.05$) from the control male x control female group. [d] Significantly different ($p<0.05$) from the 0.4% male x control female group[e] One litter had no live male pups. [f] One litter had no live female pups. [g] Least squares estimate of mean pup weight adjusted for average litter size±SE

In the F1 reproduction study (Task 4) a dose-related decrease was noted with respect to the average number of live pups per litter. The proportion of pups born alive and average pup weight was not affected by treatment with the substance ($p>0.05$). The adjusted pup weight values were significantly decreased ($p<0.05$) at the highest dose level.

Reproductive Performance of Second Generation Fertile Pairs (F1, Task 4)

| Reproductive Parameter [a] | Treatment Group | | | |
|---|---|---|---|---|
| | Control Male x Control Female | 0.1% Male x 0.1% Female | 0.2% Male x 0.2% Female | 0.4% Male x 0.4% Female |
| Live Pups per Litter | | | | |
| Male | 6.42±0.55 (19)[b] | 5.44±0.34 (18)[c] | 5.89±0.60 (18) | 3.89±0.51 (18)[d] |
| Female | 5.58±0.47 (19) | 6.22±0.32 (18) | 4.44±0.70 (18) | 4.17±0.54 (18) |
| Combined | 12.00±0.50 (19) | 11.67±0.43 (18) | 10.33±1.09 (18) | 8.06±0.65 (18)[d] |
| Proportion of Pups Born Alive | 1.00±0.00 (19) | 1.00±0.00 (18) | 0.94±0.06 (18) | 0.99±0.01 (18) |
| Sex of Pups Born Alive (Male/Total) | 0.53±0.04 (19) | 0.46±0.02 (18) | 0.61±0.04 (17)[e] | 0.47±0.05 (18) |
| Live Pup Weight (g) | | | | |
| Male | 1.57±0.02 (19) | 1.57±0.03 (18) | 1.56±0.05 (17) | 1.48±0.03 (17)[c,f] |
| Female | 1.52±0.03 (19) | 1.52±0.02 (18) | 1.51±0.05 (16)[g] | 1.50±0.05 (18) |
| Combined | 1.55±0.02 (19) | 1.54±0.02 (18) | 1.55±0.05 (17) | 1.50±0.04 (18) |
| Adjusted Live Pup Weight (g)[e] | | | | |
| Male | 1.61±0.03 (19) | 1.60±0.03 (18) | 1.57±0.03 (17) | 1.40±0.03 (17)[d] |
| Female | 1.57±0.03 (19) | 1.55±0.03 (18) | 1.53±0.03 (16)[g] | 1.39±0.03 (18)[d] |
| Combined | 1.60±0.02 (19) | 1.58±0.02 (18) | 1.55±0.03 (17) | 1.40±0.03 (18)[d] |

[a] Mean±SE. [b] Number of fertile pairs providing the data indicated in parenthesis. [c] Significantly different ($p<0.05$) from the control group. [d] Significantly different ($p<0.01$) from the control group. [e] One litter contained no live pups. [f] One litter contained no live male pups. [g] One litter contained no live female pups. [h] Least squares estimate of mean pup weight adjusted for average litter size±SE

- **Viability index (pups surviving 4 days/total births) and survival at 14 days:** The final litter (Task 2) from the control and all 3 dose groups was kept to check the effect of the substance on pup survival. Treatment had no apparent effect on pup survival, although it should be stressed that the average litter sizes in the 0.2 and 0.4% dose groups were significantly smaller ($p<0.05$) apparently due to the toxicity of the test substance. Viability index was not calculated in the study report.

Summary of Pup Survival (Task 2, Final litter)

| Parameter [a] | | Treatment Group | | | |
|---|---|---|---|---|---|
| | | Control | 0.1% | 0.2% | 0.4% |
| Number of Breeding Pairs | | 40 | 20 | 19 | 19 |
| Number of Litters Born | | 38 | 19 | 18 | 19 |
| Total Live Pups per Litter | | | | | |
| Age (days) | 0 | 12.29±0.51 (38)[b] | 13.32±0.64 (19) | 11.00±0.64 (18) | 5.74±0.88 (19)[c] |
| | 4 | 11.08±0.59 (38) | 11.32±1.19 (19) | 10.33±0.67 (18) | 5.00±0.95 (19)[c] |
| | 14 | 10.66±0.67 (38) | 10.95±1.15 (19) | 10.41±0.67 (17)[d] | 4.95±0.93 (19)[c] |
| Live Male Pups per Litter | | | | | |
| Age (days) | 0 | 6.03±0.44 (38) | 6.42±0.51 (19) | 5.22±0.53 (18) | 3.16±0.54 (19)[c] |
| | 4 | 5.32±0.42 (38) | 5.47±0.68 (19) | 4.83±0.50 (18) | 2.84±0.59 (19)[c] |
| | 14 | 5.16±0.46 (38) | 5.21±0.63 (19) | 4.94±0.52 (17)[d] | 2.84±0.59 (19)[e] |
| Live Female Pups per Litter | | | | | |
| Age (days) | 0 | 6.26±0.40 (38) | 6.89±0.51 (19) | 5.78±0.47 (18) | 2.58±0.50 (19)[c] |
| | 4 | 5.76±0.42 (38) | 5.84±0.78 (19) | 5.50±0.45 (18) | 2.16±0.52 (19)[c] |
| | 14 | 5.50±0.44 (38) | 5.74±0.75 (19) | 5.47±0.46 (17)[d] | 2.11±0.49 (19)[e] |

[a] Mean±SE. [b] Number of fertile pairs providing the data indicated in parenthesis. [c] Significantly different ($p<0.01$) from the control group. [d] One litter, along with the dam, was sacrificed on postnatal day 9 as per instructions of veterinarian in charge. [e] Significantly different ($p<0.05$) from the control group

- **Effects on offspring (grossly visible abnormalities):** None
- **Postnatal growth, growth rate:** No data
- **Vaginal opening (F) or preputial separation (M):** No data
- **Other observations, for instance anogenital distance, if measured:** No data
- **Organ weights:** No data for F2
  - **Gross pathology:** No data for F2

**CONCLUSIONS**

**Remarks:** The substance administered in feed at the 0.4% dose level adversely affected reproduction in CD-1 mice. Continued treatment at this dose level also resulted in a significant drop in body weight. The crossover mating study showed that it was the reproductive performance of female mice that was affected by treatment with the substance at the 0.4% dose level. The number of live pups per litter delivered by the 0.4% female x control male group being significantly lower than the 0.4% male x control female group. The reproductive performance of second generation CD-1 mice exposed to the substance at the 0.4% dose level was adversely affected with respect to the number of live pups per litter and the adjusted live pup weight. Second generation animals in the 0.4% group weighed less than the control group at weaning, through maturation and at necropsy.

**DATA QUALITY**

- **Reliabilities:** 1, Valid without restrictions

**Remarks:** Well-conducted study performed by Environmental Health Research and Testing, Inc.

**REFERENCES (Free Text)**

Gulati, D.K., et al, Environmental Health Research & Testing, Inc., 2,2-bis(bromomethyl)-1,3-propanediol: Reproduction and fertility assessment in CD-1 mice when administered in feed, NTP Contract # N01-ES-2-5013, Report No. NTP-86-063, January 1986

Treinen, K.A., et al, Reproductive toxicity of 2,2-bis(bromomethyl)-1,3-propanediol in a continuous breeding protocol in Swiss (CD-1) mice, Fundamental & Applied Toxicology, 13, 245-255, 1989

**OTHER**

- Last Changed: October 4 2002
- Order number for sorting: 1

**Remarks:**